Protocol: A double-blind, placebo-controlled, fixed dose study of AGN-241751 in adult participants with major depressive disorder, Amendment 2

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# Title Page

**Protocol Title:** A Double-Blind, Placebo-Controlled, Fixed-Dose Study of AGN-241751 in Adult Participants with Major Depressive Disorder

**Brief Protocol Title:** AGN-241751 in the treatment of major depressive disorder

**Product:** AGN-241751

**Sponsor Name and Legal Registered Address:** Naurex, Inc., an indirect subsidiary of Allergan plc, 5 Giralda Farms Madison, NJ 07940 USA

**Regulatory Agency Identifying Number:** IND 129,495

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**Protocol Amendment Summary of Changes Table**

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| Amendment 2 | 01 May 2019 |
| Amendment 1 | 08 Jun 2018 |
| Original Protocol | 02 Mar 2018 |

**Protocol Amendment 2:** May 2019

**Overall Rationale for the Amendment:**

The protocol was amended to incorporate regulatory agency feedback on statistical analysis.

| Section No. and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1 Synopsis | Added that framework for estimands will be discussed in Section 10.1 | Based on updated regulatory requirements for statistical analysis that requires inclusion of estimands. |
| 4. Objectives and Endpoints | This section was updated to clarify endpoints for the additional analysis to include all days where MADRS, CGI-S, etc were evaluated that were not part of primary or secondary analysis | Clarification to the protocol |
| 10.1 Estimands Framework | This section was added, including subsections, and provides an estimand framework for the primary and secondary endpoints | As above |
| 10.4.1 Efficacy Analysis | Removed LOCF calculations and changed small center will be defined as a center with fewer than 2 participants (instead of 5 participants) in the mITT Population | As above and to align with other studies in the program |
| 10.4.1.1 Primary and Secondary Endpoint | Added reference to estimands | As above |
| 10.4.1.2 Primary and Secondary Analysis | Updated statistical methods, including removal of LOCF and ANCOVA from analysis and replaced with a sensitivity analysis using the MI approach under MNAR assumptions | As above |
| 10.4.2.2 Clinical Laboratory | Clarified language regarding non-PCS baseline values | Clarification |

| Section No. and Name | Description of Change | Brief Rationale |
|---|---|---|
| Assessments | | |
| 10.4.2.3 Vital Signs | Clarified language regarding non-PCS baseline values | Clarification |
| 12.1 Appendix 1 | Updated abbreviations based on changes to body | To align with other changes in the protocol |
| 12.5 Appendix 5 | Removed bilateral tubal ligation as the type of surgical sterilization for female partners of male study subjects. | To align with other studies in the program. |

# Table of Contents

# List of Figures

# 1. Synopsis

**Protocol Title:** A Double-Blind, Placebo-Controlled, Fixed-Dose Study of AGN-241751 in Adult Participants with Major Depressive Disorder

**Protocol Number:** 3125-201-002

**Brief Title:** AGN-241751 in the treatment of major depressive disorder

**Study Phase:** 2a

**Study Rationale:**

AGN-241751 is a functional modulator of the N-methyl D-aspartate receptor (NMDAR) with partial agonist properties. In rodent models of depression, AGN-241751 elicited potent, rapid, and long-lasting antidepressant activity without adverse central nervous system (CNS) effects. AGN-241751 is an orally bioavailable small molecule with NMDAR partial co-agonist pharmacology. Thus, it represents a novel pharmacology that may address a significant unmet need with minimal side effects and the feasibility of an oral dosage form. This is a proof-of-concept study of AGN-241751 monotherapy in the treatment of major depressive disorder (MDD).

**Objectives and Endpoints:**

The primary objective is to evaluate the efficacy, as measured by improvement in Montgomery-Åsberg Depression Rating Scale (MADRS) total score, at 1 day post initial oral dose of AGN-241751 compared with placebo in participants with MDD. The key secondary objective is to evaluate the efficacy at Week 3 of AGN-241751 administered orally once a week compared with placebo in participants with MDD.

| Objectives | Endpoints |
|---|---|
| Primary | |
| • To evaluate the efficacy at 1 day post initial oral dose of AGN-241751 compared with placebo in participants with MDD | • Change from baseline in MADRS total score at 1 day after first dose |
| Key Secondary | |
| • To evaluate the efficacy at Week 3 of AGN-241751 administered orally once a week compared with placebo in participants with MDD | • Change from baseline in MADRS total score at Week 3 |

The framework of estimands for this study is presented in Section 10.1

**Overall Study Design:**

This study is a multicenter, randomized, double-blind (with a single-blind placebo lead-in), placebo-controlled, parallel-group, fixed-dose, 3-week study in participants with MDD. The study will include a total of 10 visits and will be approximately 5 weeks in duration:

- Up to 1-week screening period
- 3-week double-blind treatment period
- 1-week safety follow-up period

After providing written consent, participants will enter a single-blind placebo lead-in screening period of up to 7 days. **Screening procedures may be conducted on up to 2 separate dates where necessary to accommodate participant and site schedule; however, every effort should be made to conduct all procedures as early as possible in the screening period and the rater-administered MADRS and computer-administered MADRS must be collected on the same date**. Participants will receive single-blind placebo during the screening period. Participants meeting the eligibility criteria at the end of Visit 2 (Baseline) will be assigned a treatment by the interactive web response system (IWRS) and enter the double-blind treatment period.

Approximately 250 participants are planned for enrollment in the double-blind treatment period (50 participants each in the AGN-241751 and placebo groups). Participants will be randomized in a ratio of 1:1:1:1:1 to 1 of 5 treatment groups: 0.25-mg, 1-mg, 3-mg, 10-mg dose AGN-241751 and placebo.

Aside from the single-blind screening period and double-blind treatment period, there is an additional single-blind element to this study (blinded to the participant). AGN-241751 is being developed for once-weekly dosing; however, in order to minimize participant's expectations and control for placebo response, treatment will be presented to participants as oral daily dosing. Each treatment kit (dispensed once weekly) in the double-blind treatment period will contain 2 bottles: Bottle 1 will contain a single dose of double-blind study treatment and Bottle 2 will contain multiple doses of single-blind placebo tablets (blinded to the participant). At Visit 2 (Day 1), Visit 5 (Day 8), and Visit 8 (Day 15), site staff will give the participant the single dose of double-blind study treatment from Bottle 1 to take by oral ingestion in the clinic (ie, the first dose of study treatment for that week). Site staff will give Bottle 2, which contains the single-blind placebo tablets, to the participant with the instruction to take 1 tablet daily by oral ingestion for the remainder of that week. To maintain consistency, study treatment at Visit 1 (single-blind placebo lead-in) will be dispensed in the same manner; the single dose of single-blind study treatment from Bottle 1 will be given to the participant for oral ingestion in the clinic, and then, Bottle 2 containing single-blind placebo tablets will be dispensed for the participant to take 1 tablet daily by oral ingestion through the remainder of the week.

During the first 2 weeks of the double-blind treatment period, participants will have 3 study visits per week. The visits will occur in the following pattern: in-clinic treatment day, 1 day

following the in-clinic treatment day, 4 days following the in-clinic treatment day, and 7 days following the in-clinic treatment day (which is the next in-clinic treatment day). If necessary, study visits may be conducted up to 2 days before or after the scheduled visits with the exception of visits that are 1 day apart (ie, Visits 2 and 3 must be conducted 1 day apart; and Visits 5 and 6 must be conducted 1 day apart). Visit 8 will be conducted 7 days following the second in-clinic treatment day. All participants who receive study treatment must complete Visit 9/Early Termination (ET) Visit. Participants will enter a 1-week safety follow-up period and return for Visit 10. Participants who prematurely discontinue from the study before completing 3 weeks of double-blind treatment should enter the 1-week safety follow-up period. Additional follow-up visits may be scheduled within 30 days, if necessary for safety reasons.

**Number of Participants:**

Approximately 250 participants who meet eligibility criteria at Visit 2 (Baseline) will be randomly assigned to study treatment such that approximately 50 participants per arm will be allocated in a 1:1:1:1:1 ratio.

**Treatment Groups and Study Duration:**

*Treatment Groups*: AGN-241751 0.25 mg, 1 mg, 3 mg, and 10 mg, and placebo

*Study Duration*: approximately 5 weeks

*Dosage Regimen*:

During the lead-in screening period of up to 7 days, participants will take 1 single-blind placebo tablet by oral ingestion once daily; the first dose will be administered in the clinic.

During the 3-week double-blind treatment period, a single tablet of double-blind study treatment (placebo, AGN-241751 0.25 mg, 1 mg, 3 mg, or 10 mg) will be administered orally once weekly in the clinic. A bottle of single-blind placebo tablets (blinded to the participant) will be dispensed for the participant to take 1 tablet once daily by oral ingestion through the remainder of that corresponding week.

**Number of Sites:**

Approximately 20 sites in the United States

## 2. Schedule of Activities (SoA)

| | Single-blind Placebo Run-In Period | Double-blind Treatment Period | | | | | | | | | Safety Follow-up Period |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Visit*** | ***1 (Screening)*** | ***2 (Baseline)*** | ***2a*** | ***3*** | ***4*** | ***5*** | ***6*** | ***7*** | ***8*** | ***9/ET[a]*** | ***10*** |
| **Study Day** | **up to -7 days** | **1** | **4 hrs post dose** | **2 (1 day post dose)** | **5** | **8** | **9** | **12** | **15** | **22** | **29** |
| Informed consent | x | | | | | | | | | | |
| Medical (surgical, neurologic) and psychiatric histories | x | | | | | | | | | | |
| Prior medication history | x | | | | | | | | | | |
| Inclusion/exclusion | x | x | | | | | | | | | |
| Randomization assessment | | x | | | | | | | | | |
| Clinical laboratory determinations[b] | x | | | | | | | | | x | |
| Urine drug screen | x | | | | | | | | | x | |
| Serum pregnancy test | x | | | | | | | | | x | |
| Vital signs[c] | x | x | x | x | x | x | x | x | x | x | x |
| ECG | x | | | | | | | | | x | |
| Physical examination | x | | | | | | | | | x | |
| DxV | x | | | | | | | | | | |
| SCID | x | | | | | | | | | | |
| MADRS | x | x | x | x | x | x | x | x | x | x | |
| CGI-S | x | x | x | x | x | x | x | x | x | x | |
| BPRS+ | x | x | | | | x | | | | x | |
| CADSS | x | x | | | | x | | | | x | |
| C-SSRS | x | x | x | x | x | x | x | x | x | x | x |
| SDC | x | | | | | | | | | x | |
| C-VISA | x | | | | | | | | | | |

| | Single-blind Placebo Run-In Period | Double-blind Treatment Period | | | | | | | | | Safety Follow-up Period |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Visit*** | ***1 (Screening)*** | ***2 (Baseline)*** | ***2a*** | ***3*** | ***4*** | ***5*** | ***6*** | ***7*** | ***8*** | ***9/ET[a]*** | ***10*** |
| **Study Day** | **up to -7 days** | **1** | **4 hrs post dose** | **2 (1 day post dose)** | **5** | **8** | **9** | **12** | **15** | **22** | **29** |
| AEs | | x | x | x | x | x | x | x | x | x | x |
| Concomitant medications | x | x | x | x | x | x | x | x | x | x | x |
| PK sampling[d] | | x (1 hr, 2 hrs, and 4 hrs post dose) | | | | x 1 sample (15 min to 3 hrs post dose) | | | | | |
| Study treatment administration in the clinic | x (single-blind placebo) | x | | | | x | | | x | | |
| Study treatment compliance | | x | | x | x | x | x | x | x | x | |

**Screening procedures may be conducted on up to 2 separate dates where necessary to accommodate participant and site schedule; however, every effort should be made to conduct all procedures as early as possible in the screening period. The rater-administered MADRS and computer-administered MADRS must be collected on the same date. At Visit 1 (Screening), the computer-administered MADRS will be conducted prior to the rater-administered MADRS. At all other visits, the rater-administered MADRS will be conducted first.**

**If necessary, study visits may be conducted up to 2 days before or after the scheduled visits except for visits that are 1 day apart (ie, Visits 2 and 3 must be conducted 1 day apart, and Visits 5 and 6 must be conducted 1 day apart).**

AE = adverse event; BPRS+ = Brief Psychiatric Rating Scale - Positive Symptoms Subscale; CADSS = Clinician Administered Dissociative States Scale; CGI-S = Clinical Global Impressions-Severity; C-SSRS = Columbia–Suicide Severity Rating Scale; C-VISA = Clinical Validation Inventory for Study Admission; DSM = *Diagnostic and Statistical Manual of Mental Disorders*; DxV = Diagnostic Validation; ECG = electrocardiogram; ET = Early Termination; MADRS = Montgomery-Åsberg Depression Rating Scale; PK = pharmacokinetic; SCID = Structured Clinical Interview for DSM disorders; SDC = Symbol Digit Coding

[a] Performed for all participants, including those prematurely discontinued after randomization. Clinically significant findings upon termination should be followed until the condition returns to prestudy status or can be explained as unrelated to study treatment. If necessary, additional follow-up visits can be scheduled.

[b] Participants will be requested to fast overnight or for at least 8 hours before arriving at the study center for appointments involving the collection of clinical

laboratory blood tests. Clinical laboratory tests can be done at any visit for safety reasons at the discretion of the investigator.

[c] Height will only be measured at Visit 1 (Screening); pulse rate, blood pressure, temperature, and body weight will be assessed at every visit. Blood pressure and pulse will be assessed while the participant is supine and standing.

[d] PK sampling is optional. For participants who consent to participate, samples will be collected at Visit 2/2a (Day 1) at 1 hour (± 15 minutes), 2 hours (± 15 minutes), and 4 hours (± 15 minutes) post dose. At Visit 5 (Day 8), a single sample will be collected any time from 15 minutes to 3 hours post dose; site staff should record the time of the prior meal taken by the participant before the PK sample collection, whenever possible.

# 3. Introduction

*Disease Burden of Major Depressive Disorder*

Major depressive disorder (MDD) is a highly disabling, serious condition which is associated with significant morbidity and mortality. MDD manifests as a major depressive episode (which may be singular or recurrent) in which the affected individual experiences 1) depressed mood, or 2) loss of interest or pleasure (as well as other symptoms) for most of the day, nearly every day, for at least 2 weeks. MDD affects approximately 14.8 million American adults, or about 6.7% of the US population 18 years of age and older, in a given year (Kessler 2005). Worldwide, about 15% of the adult population is at lifetime risk of developing MDD (Kessler 1994).

Depression may cause serious, long-lasting symptoms and often disrupts a person's ability to perform routine tasks. In 2000, unipolar depressive disorders were by far the leading cause (11.9%) of worldwide years of life lived with disability (World Health Organization, 2001), and the total economic burden of treating depression in the United States was $83.1 billion, with workplace costs, including missed days and lack of productivity due to illness, accounting for most of the total economic burden (62%). Other economic burdens in 2000 included $26.1 billion (31%) for treatment costs and $5.4 billion (7%) for suicide-related costs (Greenberg 2003).

MDD is a leading cause of disability in the United States (Murray 2013). Moreover, MDD is known to be a significant risk factor for suicide and ischemic heart disease, as it accounted for 16 million of the disability adjusted life years (DALYs) associated with suicide and 4 million of the DALYs associated with ischemic heart disease. Research has shown that untreated depression has both a functional (social and work role) as well as a neuroanatomical (hippocampal shrinkage) effect on the patient (Videbech and Ravnkilde 2004). Given the disease burden and link to suicidality as well as increased mortality with other comorbid conditions, MDD is a serious and life-threatening condition which is a leading cause of disability in the world.

*Selective Serotonin Reuptake Inhibitors and Selective Serotonin **and** Norepinephrine Reuptake Inhibitors in Major Depressive Disorder*

Selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and norepinephrine reuptake inhibitors (SNRIs) currently represent the first line of treatment of depression in the United States. Unfortunately, a large number of patients do not experience therapeutic benefit from these first-line agents (Rosenzweig-Lipson 2007). Lack of sufficient response to adequate treatment remains a critical problem in the management of patients with MDD. Up to two-thirds of patients treated with first-line antidepressant monotherapy do not reach full remission, and as many as a third become treatment resistant (Fava and Davidson 1996; Trivedi 2006). Not achieving remission has been shown to be predictive of poorer psychosocial functioning, higher rates of relapse, and higher rates of rehospitalization (McIntyre and O'Donovan 2004).

The results of the STAR*D study suggest that with successive failures of treatment, patients are less and less likely to respond to subsequent treatment, and those who do respond are more likely to relapse (Rush 2006). Present strategies available to treat patients who do not respond to first-line antidepressant monotherapy include switching of antidepressant (either within or between classes); combination therapy in which multiple antidepressants are used simultaneously; augmentation of ongoing antidepressant monotherapy with adjunctive use of drugs such as mood stabilizers or atypical antipsychotics (Boland and Keller 2006); and nonpharmacologic treatments including psychotherapy and phototherapy, vagus nerve stimulation, transcranial magnetic stimulation, and electroconvulsive therapy (ECT). Clearly, there remains a critically important unmet medical need for this patient population.

Existing antidepressants have a number of limitations, leading to considerable unmet medical need in the effective treatment of MDD, with up to 50% of patients with MDD having an inadequate response or failing current antidepressant therapy (ADT). Currently available first-line antidepressants (SSRIs, SNRIs) typically take 3 to 4 weeks or more of continuous daily dosing to relieve symptoms of MDD and are associated with side effects related to their pharmacological mechanisms of action (sexual dysfunction, weight gain, jitteriness, sleep disturbances), which are further associated with poor patient compliance (Masand 2003, Ashton 2005). Patients often experience undesirable side effects before they experience an improvement in depressive symptoms, which could lead to premature discontinuation of therapy. Taken together, these factors define significant areas for improvement of ADT.

Patients vary greatly in their response to antidepressants and it is not possible to reliably predict whether an individual patient will respond to a given antidepressant. This leads to clinicians often using a trial-and-error approach to identify an effective antidepressant. Due to the slow onset of the development of the full therapeutic effect of currently available treatments, each antidepressant needs to be administered for 4 weeks or longer to determine the individual therapeutic benefit, making the process of finding an effective antidepressant a lengthy process for patients who are often severely depressed and at a high risk for suicide. Clearly a drug that could induce a rapid antidepressant effect would represent a major advancement for these patients.

While inhibition of serotonin reuptake improves the management of patients with depression, these agents suffer two severe limitations: 1) they require several weeks of continued dosing until a patient can experience the full therapeutic benefit, and during this time patients continue to be affected by the symptoms of depression and the risk of self-harm, and 2) a large number of patients do not experience therapeutic benefit (Rosenzweig-Lipson 2007). Intravenous ketamine, an NMDAR antagonist, provides rapid relief of depressive symptoms, unlike the SSRIs and SNRIs; however, this beneficial effect is accompanied by classic NMDAR antagonist effects, including psychotomimetic activity, confusion, and dissociation. In addition, ketamine is approved as an anesthetic agent, and not approved for use as an antidepressant. Psychiatric use of ketamine may be limited by the need for repeated infusions to maintain a treatment response, its safety profile, and its abuse potential, being a Schedule III controlled substance. Based upon the

available evidence of ketamine, modulation of the NMDAR is being pursued as a therapeutic target for MDD treatment.

Recently, rapastinel has emerged as a representative of a potentially new class of antidepressants that positively modulate the NMDAR function and have the potential to provide rapid and significant antidepressant activity without many of the adverse side effects of NMDAR antagonists like ketamine. Rapastinel has demonstrated rapid and long-lasting antidepressant effects in rodent models of depression as well as in MDD patients, with a favorable side-effect profile (Burgdorf 2013; Preskorn 2015). Rapastinel's unique mechanism of action may explain its lack of ketamine-like side effects. Rapastinel is believed to activate a cascade of biochemical and physiological processes like long-term potentiation (LTP)-based synaptic plasticity. Rapastinel potentiates LTP following acute treatment (unlike ketamine) and does not impair cognition in a variety of animal models of cognition (unlike ketamine and other NMDAR antagonists like PCP and MK-801) (Blanke 2009; Nicholson 2009; Skolnick 2009). Early Phase 2 clinical trial experience suggests that the rapastinel pharmacology lacks the negative symptomatic effects of NMDAR antagonists. Compared with ketamine and other NMDAR antagonists, rapastinel exhibits a significantly improved central nervous system (CNS) tolerability profile.

Like rapastinel, AGN-241751 is a novel NMDAR modulator with partial agonist properties. AGN-241751 has appropriate oral bioavailability and blood brain barrier penetration.

In support of AGN-241751 investigation in human subjects, a series of nonclinical pharmacology studies have been performed. These studies were designed to characterize AGN-241751 in terms of its potential to a) potentiate NMDAR activity; b) strengthen NMDAR-dependent LTP; and c) produce antidepressant-like effects in rat models. Additional safety and tolerability studies were carried out to evaluate AGN-241751's side effect profile, including potential ataxic/sedative and pro-convulsive effects. Besides displaying potent partial agonist activity at NMDAR, AGN-241751 increased NMDAR-dependent synaptic plasticity in rat hippocampus and medial prefrontal cortex in vitro and ex vivo. AGN-241751 was active in several models of depression, and has demonstrated rapid onset of action in rat models of depression without causing CNS side effects. AGN-241751 had no appreciable affinity for over 60 neurotransmitter-receptors and ion channels in a CEREP screen indicating a lack of potential off-target effects. Central nervous system safety and tolerability profile of AGN-241751 was favorable at substantially higher doses relative to its antidepressant doses. Although transient lowering of blood pressure in conscious telemetered dogs was observed in cardiovascular safety studies, there were no findings that preclude its use for further development. In other safety pharmacology studies, AGN-241751 was not associated with any adverse effects. In summary, the safety profile of AGN-241751 supports the proposed clinical doses in Phase 2a (0.25 mg to 10 mg).

Following oral administration, mean oral bioavailability of AGN-241751 in rats and dogs was approximately 100% and 99%, respectively. There was no accumulation after repeat administration and AGN-241751 was rapidly distributed to the target tissue (brain) with time to

reach maximum concentration ($T_{max}$) at 1 hour post dose in rats. Brain to plasma and cerebrospinal fluid (CSF) to plasma area under the concentration-time curve (AUC) ratios were 0.16 and 0.3, respectively.

Acute dosing in rats showed no effects on the central or peripheral nervous system. Drug-related findings after oral dosing in rats for 28 days were limited to mild increases in absolute and relative (to brain and body) liver weights that correlated with minimal hepatocellular hypertrophy, minimal to mild pigmented material in bile ducts, and minimal periductal mononuclear cell infiltrates at ≥ 300 mg/kg/day. The no-observed-adverse-effect level (NOAEL) in this study was 600 mg/kg/day. Oral dosing in dogs was not tolerated at ≥ 40 mg/kg/day. Drug-related findings in dogs included decreases in body weight and alterations in serum chemistry (only males) at 20 mg/kg/day, reversible increases in hepatic enzymes and brown pigmented material in hepatic sinusoids at ≥ 10 mg/kg/day and minimal to moderate Kupffer cell hypertrophy/hyperplasia and minimal to mild increased incidence of mononuclear cell infiltrates at all doses. Increases in liver enzymes correlated with microscopic findings of hepatotoxicity at 20 mg/kg/day. The NOAEL was 10 mg/kg/day; however, the more conservative dose of 3 mg/kg/day is used for the calculation of safety margins due to moderate liver enzymes increases observed at 10 mg/kg/day. A dose of 3 mg/kg/day in dogs (the most sensitive species) results in a systemic exposure (AUC; Day 1) that is 3.5 times the exposure at the highest dose (50 mg) evaluated in the single ascending dose study.

Preliminary data from ongoing clinical studies, a single ascending dose study (3125-101-009) and multiple ascending dose study (3125-102-009) in healthy male and female volunteers, have demonstrated an acceptable safety and tolerability profile up to doses of 50 mg administered once, or 25 mg administered daily for consecutive 10 days. Based upon preliminary PK data in healthy volunteers, systemic exposures of AGN-241751 demonstrate rapid absorption, rapid clearance, and dose-related increases in exposures in plasma and CSF. Female subjects demonstrated similar PK exposures to male counterparts receiving a 1.0 mg dose of AGN-241751 under fasted conditions, hence sex does not appear to significantly influence the overall exposures of AGN-241751. After multiple doses of AGN-241751, no apparent systemic accumulation was observed up to 25 mg. Although the systemic exposures of AGN-241751 were slightly delayed when dosed in the fed state (approximate 40% reduction in $C_{max}$, and 1-hour delay in $T_{max}$), the overall exposures were similar for the plasma (AUC), and CSF profiles. Hence, administration of AGN-241751 can be in the fed or fasted state.

## 3.1. Study Rationale

AGN-241751 is a functional modulator of the NMDAR with partial agonist properties. In rodent models of depression, AGN-241751 elicited potent, rapid, and long-lasting antidepressant activity without adverse CNS effects. AGN-241751 is an orally bioavailable small molecule with NMDAR partial co-agonist pharmacology. Thus, it represents a novel pharmacology that may address a significant unmet need with minimal side effects and the feasibility of an oral dosage form. This is a proof-of-concept study of AGN 241751 monotherapy in the treatment of MDD.

## 3.2. Background

AGN-241751 is a novel NMDAR modulator with partial agonist properties and high oral bioavailability. Unlike the NMDAR antagonist, ketamine, AGN-241751 potentiates NMDAR function (Study BIO-16-1126, Study DMP-2015-003). AGN-241751 has the potential to provide rapid and significant antidepressant activity, unlike SSRIs and SNRIs that require several weeks of continued dosing to experience full therapeutic benefit. The compound is being developed for the treatment of MDD.

## 3.3. Benefit/Risk Assessment

The expected benefits of AGN-241751 are potentially a rapid-onset, and long-acting, oral treatment for depression. The compound has the potential to have lower side effects than what is currently on the market.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of AGN-241751 can be found in the investigator's brochure.

## 4. Objectives and Endpoints

The primary objective is to evaluate the efficacy, as measured by improvement in MADRS total score, at 1 day post initial oral dose of AGN-241751 compared with placebo in participants with MDD. The key secondary objective is to evaluate the efficacy at Week 3 of AGN-241751 administered orally once a week compared with placebo in participants with MDD.

| Objectives | Endpoints |
|---|---|
| Primary | |
| • To evaluate the efficacy at 1 day post initial oral dose of AGN-241751 compared with placebo in participants with MDD | • Change from baseline in MADRS total score at 1 day after first dose |
| Key Secondary | |
| • To evaluate the efficacy at Week 3 of AGN-241751 administered orally once a week compared with placebo in participants with MDD | • Change from baseline in MADRS total score at Week 3 |
| Additional | |
| • Additional endpoints to be explored to determine differences between AGN-241751 vs. placebo | • Change from baseline in MADRS total score at 4 hours post dose, and on Study Days 5, 8, 9, 12, and 15<br>• Change from baseline in Clinical Global Impressions-Severity (CGI-S) at 4 hours post dose, and on Study Days 2, 5, 8, 9, 12, 15, and 22<br>• Rate of sustained responders during treatment<br>• Rate of responders at 4 hours post dose, and on Study Days 2, 5, 8, 9, 12, 15, and 22<br>• Rate of sustained remitters during treatment<br>• Rate of remitters at 4 hours post dose, and on Study Days 2, 5, 8, 9, 12, 15, and 22<br>• Time to first response<br>• Time to first sustained response<br>• Time to first remission<br>• Time to first sustained remission |

| Objectives | Endpoints |
|---|---|
| Safety Measures | • Adverse event (AE) recording, clinical laboratory measures, vital sign parameters, electrocardiograms (ECGs), and physical examinations<br>• Measure of psychotomimetic effects: Brief Psychiatric Rating Scale Positive Symptoms subscale (BPRS+)<br>• Measure of dissociative effects: Clinician Administered Dissociative States Scale (CADSS)<br>• Measure of suicidality: Columbia-Suicide Severity Rating Scale (C-SSRS)<br>• Measure of cognition/psychomotor function: Symbol Digit Coding (SDC) |

**Clinical Hypotheses**

Once-weekly administration of AGN-241751 will result in greater improvement of symptoms in participants with MDD compared with placebo, as measured by the MADRS total score.

# 5. Study Design

## 5.1. Overall Design

This study is a multicenter, randomized, double-blind (with a single-blind placebo lead-in), placebo-controlled, parallel-group, fixed-dose, 3-week study in participants with MDD. The study will include a total of 10 visits and will be approximately 5 weeks in duration:

- Up to 1-week screening period
- 3-week double-blind treatment period
- 1-week safety follow-up period

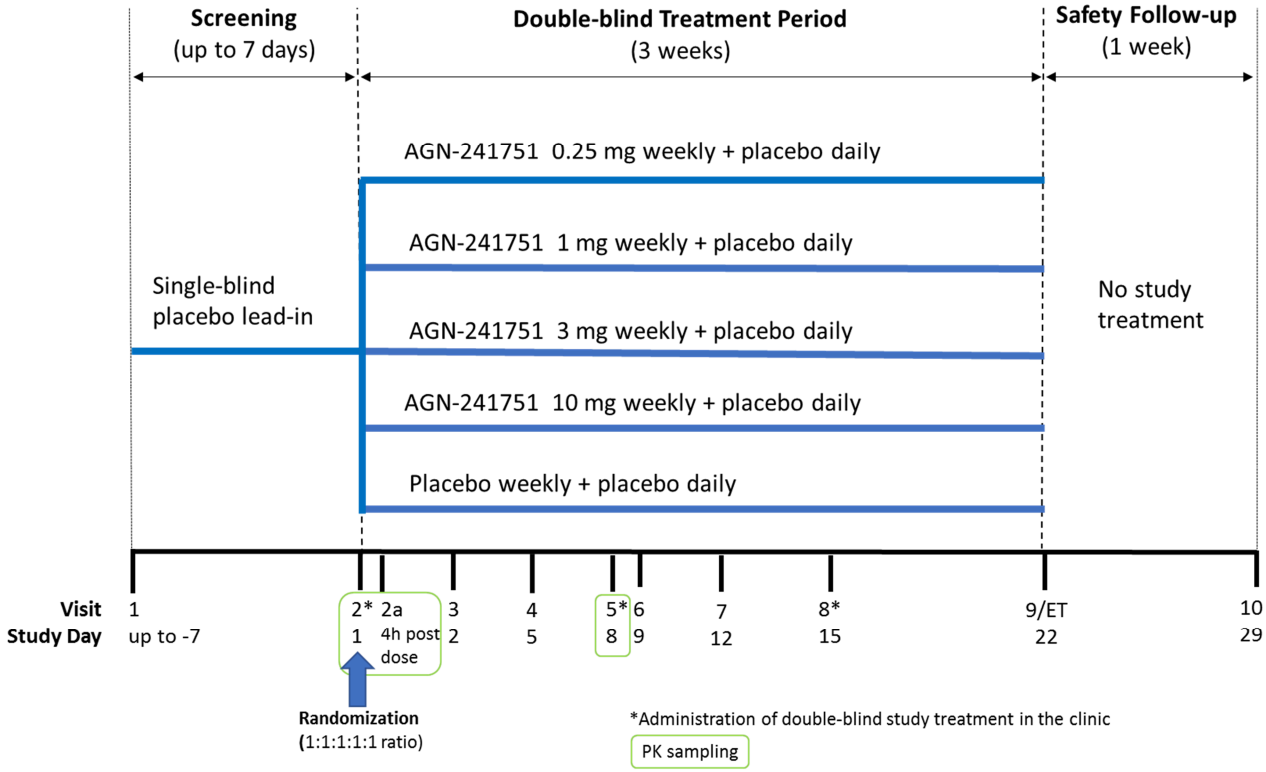
After providing written consent, participants will enter a single-blind placebo lead-in screening period of up to 7 days. **Screening procedures may be conducted on up to 2 separate dates where necessary to accommodate participant and site schedule; however, every effort should be made to conduct all procedures as early as possible in the screening period and the rater-administered MADRS and computer-administered MADRS must be collected on the same date.** Participants will receive single-blind placebo during the screening period. Participants meeting the eligibility criteria at the end of Visit 2 (Baseline) will be assigned a treatment by the interactive web response system (IWRS) and enter the double-blind treatment period.

Approximately 250 participants are planned for enrollment in the double-blind treatment period (50 participants each in the AGN-241751 and placebo groups). Participants will be randomized in a ratio of 1:1:1:1:1 to 1 of 5 treatment groups: 0.25 mg, 1 mg, 3 mg, 10 mg dose AGN-241751 and placebo.

Aside from the single-blind screening period and double-blind treatment period, there is an additional single-blind element to this study (blinded to the participant). AGN-241751 is being developed for once-weekly dosing; however, in order to minimize participant's expectations and control for placebo response, treatment will be presented to participants as oral daily dosing. Each treatment kit (dispensed once weekly) in the double-blind treatment period will contain 2 bottles: Bottle 1 will contain a single dose of double-blind study treatment and Bottle 2 will contain multiple doses single-blind placebo tablets (blinded to the participant). At Visit 2 (Day 1), Visit 5 (Day 8), and Visit 8 (Day 15), site staff will give the participant the single dose of double-blind study treatment from Bottle 1 to take by oral ingestion in the clinic (ie, the first dose of study treatment for that week). Site staff will give Bottle 2, which contains the single-blind placebo tablets, to the participant with the instruction to take 1 tablet daily by oral ingestion for the remainder of that week. To maintain consistency, study treatment at Visit 1 (single-blind placebo lead-in) will be dispensed in the same manner; the single dose of single-blind study treatment from Bottle 1 will be given to the participant for oral ingestion in the clinic, and then, Bottle 2 containing single-blind placebo tablets will be dispensed for the participant to take 1 tablet daily by oral ingestion through the remainder of the week.

During the first 2 weeks of the double-blind treatment period, participants will have 3 study visits per week. The visits will occur in the following pattern: in-clinic treatment day, 1 day following the in-clinic treatment day, 4 days following the in-clinic treatment day, and 7 days following the in-clinic treatment day (which is the next in-clinic treatment day). If necessary, study visits may be conducted up to 2 days before or after the scheduled visits with the exception of visits that are 1 day apart (ie, Visits 2 and 3 must be conducted 1 day apart; and Visits 5 and 6 must be conducted 1 day apart). Visit 8 will be conducted 7 days following the second in-clinic treatment day. All participants who receive study treatment must complete Visit 9/ET. Participants will enter a 1-week safety follow-up period and return for Visit 10. Participants who prematurely discontinue from the study before completing 3 weeks of double-blind treatment should enter the 1-week safety follow-up period. Additional follow-up visits may be scheduled within 30 days, if necessary for safety reasons.

**Figure 5–1 Study Design Diagram**




All study treatment will be administered orally

## 5.2. Participant and Study Completion

Approximately 250 participants who meet eligibility criteria at Visit 2 (Baseline) will be randomly assigned to study treatment such that approximately 50 participants per arm will be allocated in a 1:1:1:1:1 ratio.

## 5.3. End of Study Definition

The end of the study is defined as the completion of enrollment and completion of all periods of the study.

A participant is considered to have completed the study if he/she has completed the double-blind treatment period of the study.

## 5.4. Scientific Rationale for Study Design

The double-blind study design was adopted to minimize systematic bias resulting from the investigator or the participant knowing the treatment being administered. Randomization is expected to minimize participant selection bias and increase baseline comparability among the treatment groups. A placebo treatment group is included in the study to comply with worldwide regulatory preferences (Laughren 2001; Gispen-de Wied 2012), since placebo-controlled superiority trials have been shown to be conducive to higher quality studies and to provide more reliable outcomes (Feifel 2008; Laughren 2001; Gispen-de Wied 2012). Additionally, randomized double-blind comparisons versus placebo are needed to permit adequate evaluation of efficacy. Comparison to a placebo treatment is also of value for distinguishing disease manifestations from adverse reactions to the study treatment (EMA guidance 2013). The use of placebo in place of the standard therapy should not cause irreversible health problems or extreme suffering (depression is recognized by the FDA as a condition in which there is substantial improvement and variability in placebo groups) (FDA Guidance for Industry: E10, May 2001).

## 5.5. Justification for Dose

The doses and regimen of AGN-241751 (0.25 mg, 1 mg, 3 mg, and 10 mg) were selected based on summation of in vitro, nonclinical pharmacology and safety studies, and clinical studies in healthy volunteers.

- Based upon scaling of preclinical and in vitro data, these doses are expected to provide similar clinical exposures that demonstrated potentiation of NMDAR activity; strengthening NMDAR-dependent LTP; and producing lasting antidepressant-like effects in rat models.
- Given the similar mechanism of activity with rapastinel and ketamine (ie, NMDA modulation), single-dose administration of AGN-241751 is expected to result in lasting improvements within MADRS scores, and therefore, justifying the weekly interval between dosing.

- Within healthy volunteers, there was evidence from multiple pharmacodynamic tests that AGN-241751 had beneficial effects on electroencephalographic parameters, such as activation and increasing dominant frequency at doses up to 25 mg.
- Compared to the available preclinical toxicology studies, the proposed top dose of 10 mg is expected to result in substantial margins below the 28-day study NOAELs designated in the rat (575-fold) and dog (10-fold).

AGN-241751 demonstrated acceptable safety and tolerability when administered in doses of 50 mg administered once or 25 mg administered daily for 10 consecutive days in healthy male and female volunteers. Hence, it is expected that the proposed top dose of 10 mg, administered weekly, will be well tolerated.

# 6. Study Population

## 6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Written informed consent from the participant has been obtained prior to any study-related procedures (as described in Appendix 3).
2. Male or female participants must be 18 to 65 years of age, inclusive, at the time of signing the informed consent.
3. Meet *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (DSM-5) criteria for MDD (based on confirmation from the modified Structured Clinical Interview for DSM disorders [SCID]), with a current major depressive episode of at least 8 weeks and not exceeding 18 months in duration at Visit 1.
4. Have a minimum score of 26 on the rater-administered MADRS and a minimum score of 24 on the computer-administered MADRS at both Visit 1 (Screening) and Visit 2 (Baseline).
5. Have a difference of no greater than 7 points between the rater-administered MADRS and computer-administered MADRS at both Visit 1 (Screening) and Visit 2 (Baseline).
6. Have a CGI-S score ≥ 4 at both Visit 1 (Screening) and Visit 2 (Baseline).
7. Have a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test if a woman of childbearing potential (WOCBP).
8. Female participants willing to minimize the risk of becoming pregnancy for the duration of the clinical study and follow-up period. A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:

   a. Not a WOCBP

   OR

   b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 5 terminal half-lives after the last dose of study treatment.

9. Male participants willing to minimize the risk of inducing pregnancy for the duration of the clinical study and follow-up period. A male participant must agree to use contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 5 terminal half-lives after the last dose of study treatment and refrain from donating sperm during this period.
10. Able, as assessed by the investigator, and willing to follow study instructions and likely to complete all required study visits.
11. Normal physical-examination findings, clinical-laboratory test results, and ECG results from Visit 1 (Screening) or abnormal results that are determined to be not clinically significant by the investigator.
12. Body mass index (BMI) within the range 18 and 40 $kg/m^2$ (inclusive).
13. Eligibility confirmed through a formal adjudication process (see Section 9 Diagnostic Assessments).

## 6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

***Psychiatric and Treatment-Related Criteria***

1. DSM-5–based diagnosis of any disorder other than MDD that was the primary focus of treatment within 6 months before Visit 1. Comorbid generalized anxiety disorder, social anxiety disorder, or specific phobias are acceptable provided they play a secondary role in the balance of symptoms and are not the primary driver of treatment decisions.
2. Lifetime history of meeting DSM-5 criteria for:
    a. Schizophrenia spectrum or other psychotic disorder
    b. Bipolar or related disorder
    c. Major neurocognitive disorder
    d. Neurodevelopmental disorder of greater than mild severity or of a severity that impacts the participant's ability to consent, follow study directions, or otherwise safely participate in the study
    e. Dissociative disorder

f. Posttraumatic stress disorder

g. MDD with psychotic features

3. History of meeting DSM-5 criteria for alcohol or substance use disorder (other than nicotine or caffeine) within the 6 months before Visit 1.

4. DSM-5–based diagnosis of any personality disorder of sufficient severity to interfere with participation in this study in the opinion of the investigator.

5. History (based on participant report and/or medical records, and investigator judgment) of:

   a. Inadequate response to ECT, a monoamine oxidase inhibitor, ketamine, or adjunctive treatment with an antipsychotic

   b. Treatment with clozapine or any depot antipsychotic

   c. ECT, vagus nerve stimulation, transcranial magnetic stimulation, or any experimental central nervous system treatment during the current episode or in the 6 months before Visit 1 (whichever is longer)

   d. Tardive dyskinesia, serotonin syndrome, or neuroleptic malignant syndrome

6. Having received:

   a. Anticonvulsant/mood stabilizer, within 1 year prior to Visit 1

   b. Antipsychotic in the current episode, with the exception of quetiapine given for insomnia ≤ 50 mg/day provided it can be safely discontinued prior to Visit 2

   c. Combination therapy of 2 or more ADTs in the current episode if given for depression at adequate dose and duration

   d. ADT augmentation agent in the current episode

7. Lifetime history of nonresponse to ≥ 2 antidepressants after adequate trials (adequate treatment is defined as at least 6 weeks at an adequate dose(s) based on approved package insert recommendations).

8. Positive result at Visit 1 from the urine drug screen (UDS) test for any prohibited medication. Exception: participants with a positive UDS at Visit 1 for opiates, cannabinoids, or episodic use of benzodiazepines may be allowed in the study provided:

a. The drug was used for a legitimate medical purpose;

b. The drug can be discontinued prior to participation in the study (except for episodic use of benzodiazepines which may be continued); and

c. A repeat UDS is negative for these substances prior to enrollment (except for episodic use of benzodiazepines which may be continued)

9. Suicide risk, as determined by meeting any of the following criteria:

   a. A suicide attempt within the past year

   b. Significant risk, as judged by the investigator, based on the psychiatric interview or information collected in the C-SSRS at Visit 1 (Screening) or Visit 2 (Baseline)

   c. MADRS Item 10 score ≥ 5 at Visit 1 (Screening) or Visit 2 (Baseline) on the MADRS

10. At imminent risk of injuring self or others or causing significant damage to property, as judged by the investigator.

11. Requiring concomitant treatment with any of the prohibited medications, supplements, or herbal products listed in Appendix 6, including any psychotropic drug or any drug with psychotropic activity, except as described in Section 7.7.2.

12. Prior participation in any investigational study of AGN-241751.

13. Initiation or termination of psychotherapy for depression within the 3 months preceding Visit 1, or plans to initiate, terminate, or change such therapy during the course of the study. (Support meetings or counseling [eg, marital counseling] are allowed provided they are no more frequent than weekly and do not have treatment of depression as their objective).

14. Ongoing treatment with phototherapy, or termination of phototherapy within 1 month of Visit 1.

15. Known allergy or sensitivity to the study medication or its components.

***Other Medical Criteria***

16. BMI < 18 kg/m$^2$ or > 40 kg/m$^2$ at screening.

17. Females who are pregnant, breastfeeding, or planning to become pregnant or breastfeed during the study.

18. WOCBP and male partners of WOCBP, not using a reliable means of contraception (Appendix 5).
19. Participant has a condition or is in a situation which, in the investigator's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study.
20. Any cardiovascular disease that is clinically significant, unstable, or decompensated.
21. Heart rate (supine) of ≤ 45 bpm or ≥ 120 bpm, or any heart rate that is clinically symptomatic at Visit 1 or Visit 2 based upon vital signs.
22. Any systolic and/or diastolic blood pressure (BP) that is symptomatic or clinically significant in the opinion of the investigator.
23. History of congenital QTc prolongation or QTc prolongation (screening ECG with QTcF ≥ 450 msec for men and QTcF ≥ 470 msec for women).
24. Hypothyroidism or hyperthyroidism, unless stabilized on appropriate pharmacotherapy with no change in dosage for at least 1 month before Visit 1.
25. History of seizure disorder, stroke, significant head injury, tumor of the central nervous system, or any other condition that predisposes to seizure.
26. Known human immunodeficiency virus (HIV) infection.
27. Positive hepatitis C antibody on screening, with the exception of participants for whom the reflex HCV RNA test is negative.
28. Positive test for hepatitis B surface antigen and/or hepatitis B core antibody immunoglobulin M.
29. Screening liver enzyme test (aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT]) results > 2 times the upper limit of normal (ULN).

***Other Criteria***

30. Current enrollment in an investigational drug or device study or participation in such a study within 6 months of entry into this study.
31. Employee, or immediate relative of an employee, of the sponsor, any of its affiliates or partners, or the study center.

32. Inability to speak, read, and understand the English language sufficiently to understand the nature of the study, to provide written informed consent, or to allow the completion of all study assessments.

## 6.3. Lifestyle Restrictions

### 6.3.1. Meals and Dietary Restrictions

None

### 6.3.2. Caffeine, Alcohol, and Tobacco

Participants should not be abusing alcohol before or throughout the duration of the study.

### 6.3.3. Activity

None

## 6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to treatment in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

# 7. Treatments

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

## 7.1. Treatments Administered

During the lead-in screening period, all participants will receive single-blind placebo tablets (participants will be blinded to lead-in treatment; site personnel will be aware that the lead-in treatment is placebo). At Visit 1 (Screening), a single dose of single-blind placebo from Bottle 1 will be given to the participant for oral ingestion in the clinic. Bottle 2, containing single-blind placebo tablets, will be dispensed for the participant to take 1 tablet daily by oral ingestion through the remainder of the week.

Study treatment kits for the double-blind treatment period will be assigned at Visit 2 (Day 1), Visit 5 (Day 8), and Visit 8 (Day 15). Each treatment kit will contain 2 bottles: Bottle 1 will contain a single dose of double-blind study treatment and Bottle 2 will contain multiple doses of single-blind placebo tablets (blinded to the participant). At Visit 2 (Day 1), Visit 5 (Day 8), and Visit 8 (Day 15), site staff will give the participant the single dose of double-blind study treatment from Bottle 1 to take by oral ingestion in the clinic (ie, the first dose of study treatment for that week). Site staff will give Bottle 2, which contains the single-blind placebo tablets, to the participant with the instruction to take 1 tablet daily by oral ingestion for the remainder of that week.

| **Study Treatment Name** | AGN-241751 | Placebo |
|---|---|---|
| **Dosage Formulation** | Tablet | Tablet |
| **Unit Dose Strengths** | 0.25 mg<br>1 mg<br>3 mg<br>10 mg | - |
| **Route of Administration** | Oral | Oral |

| Study Treatment Name | AGN-241751 | Placebo |
|---|---|---|
| **Dosing Instructions** | First dose from Bottle 1 given by site staff to the participant for oral ingestion in the clinic; Bottle 2 will be given to participant to take home with instructions to take 1 tablet orally every day for the rest of the week<br>Note: study treatment will be dispensed once a week for a total of 3 weeks (at Visits 2, 5, and 8) | First dose from Bottle 1 given by site staff to the participant for oral ingestion in the clinic; Bottle 2 will be given to participant to take home with instructions to take 1 tablet orally every day for the rest of the week<br>Note: study treatment will be dispensed once a week for a total of 3 weeks (at Visits 2, 5, and 8) |
| **Packaging and Labeling** | Allergan will provide study treatment in the form of identically appearing tablets containing AGN-241751 doses of 0.25 mg, 1 mg, 3 mg, 10 mg, or placebo.<br>All participants will receive single-blind placebo tablets for the run-in period. | Allergan will provide study treatment in the form of identically appearing placebo tablets.<br>All participants will receive single-blind placebo tablets for the run-in period. |
| **Manufacturer** | Allergan, Inc. | Allergan, Inc. |

## 7.2. Dose Modification

Dose modification is not allowed.

## 7.3. Method of Treatment Assignment

All participants will be centrally assigned to randomized study treatment using an IWRS. Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site.

Study treatment will be dispensed at the study visits summarized in the schedule of activities (Section 2).

Returned study treatment should not be re-dispensed to the participants.

## 7.4. Blinding/Masking

The IWRS will be programmed with blind-breaking instructions. The study blind may be broken if, in the opinion of the investigator, it is in the participant's best interest to know the study treatment assignment. The sponsor must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the participant's condition (eg, antidote is available). In this case, the sponsor must be notified within 24 hours

after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

## 7.5. Preparation/Handling/Storage/Accountability

1. All study treatment will be provided and shipped to the study centers by Allergan Inc., and must be stored in an appropriate secure area (eg, a locked cabinet in a locked room) at refrigerate conditions (5°C with a permitted range of 2°C-8°C) and must be protected from heat and moisture.
2. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
3. Only participants enrolled in the study may receive study treatment, and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
4. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
5. Further guidance and information for the final disposition of unused study treatment are provided in the study reference manual.

## 7.6. Treatment Compliance

Compliance with administration of double-blind study treatment in the clinic at Visits 2, 5, and 8 will be monitored by capturing the date that the participant ingested the double-blind study treatment at each of these visits. If a scheduled ingestion does not occur, the sponsor must be notified and the reason captured in the eCRF.

Compliance with study treatment dosing by the participant outside of the clinic will be monitored by counting the number of tablets dispensed and returned. Before dispensing new study treatment, study center personnel will make every effort to collect all unused study treatment and empty bottles. If a participant demonstrates poor compliance at any time during the study (< 80% or > 120% measured by pill counts), the investigator should evaluate whether the participant should be discontinued from the study.

The study centers will keep an accurate drug disposition record that specifies the amount of study treatment administered to each participant and the date of administration.

## 7.7. Concomitant Therapy

The use of any concomitant medication, prescription or over-the-counter, is to be recorded on the participant's eCRF at each visit along with the reason the medication is taken.

### 7.7.1. Prohibited Treatments

Participants must discontinue any of the medications listed below for the specified period prior to baseline. These medications are prohibited for the duration of the study. Other medications being used at screening may be continued.

The following medications are prohibited:

- Antipsychotics
- Antidepressants
- Stimulants
- Anticonvulsants/mood stabilizers
- Dopamine-releasing drugs or dopamine agonists
- Psychotropic drugs not otherwise specified (including herbal products, such as St. John's Wort, and certain nutritional supplements)

See Appendix 6 Concomitant Medications for a comprehensive list of prohibited medications and allowed medication usage. Appropriate washout of prohibited medications is to be conducted at the discretion of the investigator and should begin as soon as practical following consent and screening.

The decision to administer a prohibited medication/treatment during the study period is done with the safety of the study participant as the primary consideration. When possible, the sponsor is to be notified before the prohibited medication/treatment is administered.

#### 7.7.2. Permitted Treatments

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Indication
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Therapy considered necessary for the participant's welfare may be given at the discretion of the investigator. If the permissibility of a specific medication/treatment is in question, please contact the sponsor.

The sponsor or designee should be contacted if there are any questions regarding concomitant or prior therapy.

**For Insomnia**

Eszopiclone, zolpidem, zolpidem extended-release, zopiclone or zaleplon for insomnia may be continued provided the medication has been used in a consistent manner for 4 weeks prior to enrollment. Following enrollment, these medications may also be introduced in participants not previously treated as necessitated by insomnia that emerges or worsens during the study. In these participants, the medications will be permitted up to 3 times a week at the following doses (not permitted within 8 hours of efficacy measures):

- Zolpidem (maximum of 10 mg/day)
- Zolpidem extended release (maximum of 12.5 mg/day)
- Zaleplon (maximum of 20 mg/day)
- Eszopiclone (maximum of 3 mg/day)
- Zopiclone (maximum of 7.5 mg/day)
- Suvorexant (maximum of 10 mg/day)

These medications must be administered before bedtime as recommended in their prescribing information. The medication must be documented on the concomitant medications page of the eCRF. No such medication is permitted within 8 hours of psychiatric or neurological assessments.

**For Anxiety or Agitation**

Episodic use of benzodiazepines up to approximately 2 mg/day lorazepam equivalent dose and for up to 3 consecutive days at a time may be given for anxiety-related conditions and agitation (not permitted within 8 hours of efficacy assessments).

## 7.8. Treatment after the End of the Study

Participants whose MDD symptoms worsen or are determined by the investigator not to be adequately controlled prior to completing the double-blind treatment period will be allowed to discontinue the study and start appropriate treatment at the investigator's discretion. This new treatment will not be provided by the sponsor.

# 8. Discontinuation/Withdrawal Criteria

Notification of early participant discontinuation from the study and the reason for discontinuation will be made to the sponsor and will be clearly documented on the appropriate case report form.

Reasons for discontinuation from the study treatment and/or the study may include the following:

- Adverse event
- Lack of efficacy
- Lost to follow-up
- Non-compliance with study drug
- Other
- Pregnancy
- Protocol deviation
- Screen failure
- Site terminated by sponsor
- Study terminated by sponsor
- Withdrawal by subject (withdrawal of consent to participate in the study)

## 8.1. Discontinuation of Study Treatment

All randomized participants who prematurely discontinue from the study, regardless of cause, should be seen for a final assessment at an ET Visit. A final assessment will be defined as completion of the evaluations scheduled for all participants at Visit 9/ET Visit. Participants who prematurely discontinue from the study before completing 3 weeks of double-blind treatment should enter the 1-week safety follow-up period.

Any participant may be withdrawn due to AE at the discretion of the investigator.

Any participant who meets any of the following criteria at any point during the study must be withdrawn from participation, due to AE(s) related to suicide:

a) A suicide attempt

b) Significant risk, as judged by the investigator, based on the psychiatric interview or information collected in the C-SSRS

c) MADRS Item 10 score $\geq 5$

In the event that a participant is withdrawn for a suicide-related AE, the participant should be referred for additional treatment or hospitalization, as clinically indicated, in addition to withdrawing the participant from the study.

Discontinuation of study treatment for abnormal liver function (criteria for potential Hy's law described in Section 9.2.6) should be considered by the investigator if the investigator believes that it is in best interest of the participant.

If a clinically significant finding is identified after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. Any new clinically relevant finding should be reported as an AE.

See the schedule of activities (Section 2) for data to be collected at the early termination visit and the safety follow-up visit.

## 8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- See the schedule of activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

## 8.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 2 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

# 9. Study Assessments and Procedures

- Study procedures and their timing are summarized in the schedule of activities (Section 2).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the schedule of activities.
- Repeat or unscheduled blood samples may be taken for safety reasons or for technical issues with the samples.

**Diagnostic Assessments**

The SCID will be administered during the screening interviews by a psychiatrist, doctoral-level clinical psychologist, or other clinician who has extensive professional training and experience in the diagnosis of mental illness and who meets the training requirements and qualification standards set by the sponsor and rater training vendor.

Participants will complete a computer-administered Diagnostic Validation (DxV) assessment at Visit 1 (Screening) prior to the rater-administered SCID, on a tablet computer provided to the study center. The DxV will collect data about the participants' history relative to lifelong history of MDD. The participant's diagnostic information, based on the responses to the computerized interview, will be reviewed by the independent clinical reviewers team appointed by the sponsor, and any uncertainty raised by the participant's responses on the diagnostic interview will be discussed with the investigator/study center clinician in order to establish confidence in the diagnosis. Participants for whom diagnostic agreement between the investigator/study center clinician and the rater vendor clinician cannot be reached, may not be appropriate for study participation.

Eligibility of potential participants will be confirmed by agreement with external clinical reviewer (Bracket), in which screening data will be obtained to evaluate psychiatric status (including MADRS, CGI-S, and SCID). Investigators will complete the Clinical Validation Inventory for Study Admission (C-VISA) worksheet as part of the adjudication process. The

SCID and MADRS will be audio recorded at the Visit 1 (Screening). The C-VISA worksheet and SCID and MADRS recordings will be reviewed by a team of independent clinical reviewers appointed by the sponsor.

## 9.1. Efficacy Assessments

The efficacy assessments (MADRS and CGI-S) will be administered by a psychiatrist, doctoral-level clinical psychologist, or other clinician who has extensive professional training and experience in the diagnosis of mental illness and who meets the training requirements and qualifications standards set by the sponsor and rater training vendor.

### 9.1.1. The Montgomery-Åsberg Depression Rating Scale

The MADRS (Montgomery and Åsberg 1979) is a clinician-rated scale (Appendix 8). The MADRS will be used to assess depressive symptomatology. Participants are rated on 10 items to assess feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty concentrating, and lack of interest. Each item will be scored on a 7-point scale. A score of 0 indicates the absence of symptoms, and a score of 6 indicates symptoms of maximum severity.

A qualified rater (ie, who meets the training requirements and qualifications set by the rater training vendor [Bracket]) at each investigational center will conduct the MADRS assessment. **The rater-administered MADRS will be used for the primary and secondary efficacy analyses.** In addition to MADRS administration by a qualified rater, each participant will complete an interactive, computer-administered MADRS interview on the dedicated study device. Data from the computer-administered interview will be compared with data derived from the rater-administered interview on an ongoing basis as part of a remote quality assurance program conducted by an independent vendor appointed by the sponsor.

At each visit with a MADRS assessment, the rater-administered MADRS interview will be audio recorded. The computer-administered interview (conducted by participant alone) will involve a series of probe and follow-up questions with multiple-choice response options. At Visit 1 (Screening), the computer administered MADRS will be conducted prior to the rater-administered MADRS. At all other visits, the rater-administered MADRS will be conducted first. At Visit 1 (Screening) and Visit 2 (Baseline), the MADRS will be administered with a look-back timeframe of 1 week. At all other evaluations, the MADRS will be administered with a look-back timeframe of "since last evaluation".

### 9.1.2. The Clinical Global Impressions-Severity

The CGI-S (Guy 1976) is a clinician-rated scale used to rate the severity of the patient's current state of mental illness compared with a patient population with MDD (Appendix 9). The patient will be rated on a scale from 1 to 7 with 1 indicating a "normal**,** not at all ill" and 7 indicating

"among the most extremely ill patients". The CGI-S will be administered by the investigator or a sub-investigator with extensive professional training and experience in assessing mental illness and qualification standards set by the sponsor and rater training vendor. At Visit 1 (Screening) and Visit 2 (Baseline), the CGI-S will be administered with a look-back timeframe of 1 week. At all other evaluations, the CGI-S will be administered with a look-back timeframe of "since last evaluation".

## 9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. Any AEs that are ongoing at the time of the final protocol-defined study visit will be followed until the condition returns to prestudy status, has resolved or stabilized, or can be explained as being unrelated to study treatment. If a follow-up visit is deemed necessary for appropriate safety surveillance, it will take place within 30 days of the final protocol-defined study visit.

### 9.2.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs from the signing of the ICF will be collected at the timepoints specified in the schedule of activities (Section 2), and as observed or reported spontaneously by study participants, until 30 days from the last dose of study treatment.

All AEs from the signing of the ICF will be collected at the timepoints specified in the schedule of activities (Section 2), and as observed or reported spontaneously by study participants, until 30 days from the last dose of study treatment.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the AE section of the eCRF.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

### 9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

### 9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs/SAEs will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3).

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will make every effort to provide the sponsor with a copy of any postmortem findings including histopathology.

New or updated information will be recorded in the originally completed eCRF.

The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

### 9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.

### 9.2.5. Pregnancy

- Site personnel must report every pregnancy in female participants, and female partners of male participants, from the time the participant signs the ICF until 30 days after the last dose of study treatment.

- Within 24 hours of learning of the pregnancy, the investigator must report the event to the sponsor on the Clinical Trial Pregnancy Form and fax or e-mail it to the SAE reporting fax number or e-mail provided on the title page of this protocol, even if no AE has occurred. The investigator should follow the procedures outlined in Appendix 5.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

### 9.2.6. Potential Hy's Law

Criteria for potential Hy's law cases are as follows:

- ALT or AST ≥ 3 × ULN AND
- Total bilirubin ≥ 2 × ULN AND
- Alkaline phosphatase < 2 × ULN

Study site personnel must report every participant who meets these potential criteria. Typically, all 3 analytes will be obtained from the same sample, but they may come from multiple samples taken within a 24-hour period. This requirement applies from the time the participant signs the ICF for the study until 30 days after the final protocol-defined study visit or the last known dose of study treatment (if the final visit does not occur).

A laboratory alert for potential Hy's laws cases will be in place, and must notify investigators and the sponsor immediately when the above criteria have been met. A potential Hy's law case must be faxed or e-mailed to the sponsor on an adverse event of interest form, as soon as possible (within 24 hours of learning of the potential Hy's law case) to the SAE fax number or e-mail shown on the title page of this protocol, even if no AE has occurred. The eCRF for potential Hy's law cases must be completed within 7 calendar days. Every effort to determine the cause of the liver enzyme abnormalities must be made, and close monitoring should be initiated in conjunction with the medical monitor and in accordance with the FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

### 9.2.7. Medication Errors

Medication error refers to any unintended error in the dosing and/or administration of the study treatment as per instructions in the protocol. Medication errors generally fall into 4 categories as follows:

- Wrong study drug
- Wrong dose (including dosing regimen, strength, form, concentration, amount)
- Wrong route of administration
- Wrong participant (ie, not administered to the intended participant)

Medication errors include occurrences of overdose and underdose of the study treatment.

## 9.3. Treatment of Overdose

Treatment of an overdose is not applicable for this study because only 1 dose of double-blind study treatment is provided per kit and that dose is administered to the participant once weekly in the clinic. AGN-241751 has a short half-life, hence, even in the event of an overdosage, the likelihood of lasting high exposures would be minimal.

## 9.4. Safety Assessments

Planned timepoints for all safety assessments are provided in the schedule of activities (Section 2).

### 9.4.1. Physical Examinations

A complete physical examination will be done at Visit 1 (Screening) and at Visit 9/ET by a professionally trained physician or health professional listed on Form FDA 1572 and licensed to perform physical examinations.

### 9.4.2. Vital Signs

Vital signs (pulse rate, systolic and diastolic blood pressure, oral or tympanic temperature, and body weight) will be assessed at every visit. Height will be assessed at Visit 1 (Screening).

Blood pressure and radial pulse rate will be measured in the supine position followed by the standing position. The standing measurements should be assessed after a sufficient amount of time (approximately 1-3 minutes) has been elapsed to allow the BP to equilibrate in the standing state.

Radial pulse rate should be measured after blood pressure measurements. Blood pressure may be measured manually or by machine, but radial pulse rate should only be measured manually and for a sufficient time to acquire an accurate measurement.

Participants should be instructed not to wear clothing with tight sleeves when they come for clinic visits. Additionally, participants should be kept as calm and undisturbed as possible while blood pressure and pulse rate measurements are taken (eg, there should be no talking while the blood pressure is being measured). The same arm and blood pressure cuff (appropriate to the arm circumference) should be used for all blood pressure measurements.

Whenever possible, the participant's weight will be measured at the same time of day; participants should wear their usual indoor clothing, but take off their jacket and shoes. For each participant, body weight should be determined using the same equipment during the study after ensuring its proper calibration.

### 9.4.3. Electrocardiograms

A 12-lead ECG will be performed at Visit 1 (Screening) and Visit 9/ET. ECGs will be performed and electronically transmitted to a central ECG laboratory for analysis according to the instructions provided by the central ECG laboratory. Measurements (in msec) will be recorded

for the following parameters: PR interval, QRS duration, and uncorrected QT interval. QTcB (Bazett corrected QT interval) and QTcF (Fridericia corrected QT interval) will be calculated.

The overall interpretation and determination of the clinical relevance of ECG findings using the central ECG interpretation laboratory report will be the responsibility of the investigator and will be recorded in the participant's eCRF.

Throughout the study, the investigator will review the central ECG reports and indicate the clinical significance of all abnormal values, and then sign and file the report in the participant's study file.

### 9.4.4. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and the schedule of activities (Section 2) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study that are considered Adverse Events per the judgment of the investigator in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the schedule of activities.
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

### 9.4.5. Columbia-Suicide Severity Rating Scale

The C-SSRS is an instrument that reports the severity of both suicidal ideation and behavior (Appendix 12 and Appendix 13). Suicidal ideation is classified on a 5-item scale: 1 (wish to be dead), 2 (nonspecific active suicidal thoughts), 3 (active suicidal ideation with any methods [not plan] without intent to act), 4 (active suicidal ideation with some intent to act, without specific plan), and 5 (active suicidal ideation with specific plan and intent). The C-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. Suicidal behavior is classified on a 5-item scale: 0 (no suicidal behavior), 1 (preparatory acts or behavior), 2 (aborted attempt),

3 (interrupted attempt), and 4 (actual attempt). More than 1 classification can be selected provided they represent separate episodes. For actual attempts only, the actual or potential lethality is classified for the initial, most lethal, and most recent attempts.

The C-SSRS will be completed at all study visits. At Visit 1 (Screening), the C-SSRS will be completed for the participant's lifetime history of suicidal ideation and behavior. At all other visits, the C-SSRS will be completed for ideation and behavior since the previous visit. The C-SSRS will be evaluated and signed at each visit by a qualified staff member (ie, the investigator or designee who has extensive professional training and experience in assessing mental illness), before the participant leaves the study center.

### 9.4.6. Brief Psychiatric Rating Scale—Positive Symptoms Subscale

The BPRS is an 18-item evaluation that assesses psychiatric symptoms and unusual behavior (Overall and Gorham 1962). The BPRS+ is a subset of the BPRS that assesses 4 components of the BPRS related to the degree of psychosis: Conceptual Disorganization, Suspiciousness, Hallucinatory Behavior, and Unusual Thought Content (Appendix 10). Only the 4 items of BPRS + subscale will be collected and analyzed. The BPRS+ will be administered by the investigator or designee with extensive professional training and experience in assessing mental illness. At Visit 1 (Screening) and Visit 2 (Baseline) the BPRS+ will be administered with a look-back timeframe of 1 week. At all other evaluations, the BPRS+ with a look-back timeframe of "since last evaluation".

### 9.4.7. Clinician Administered Dissociative States Scale

The CADSS is a 28-item clinician-administered measure of perceptual, behavioral, and attentional alterations occurring during active dissociative experiences composed of 23 subjective self-reported and 5 objective observer-reported ratings, each scored from 0 (not at all) to 4 (extremely) (Appendix 11). Only the 23 subjective items will be collected and analyzed. The CADSS provides a validated assessment of dissociative states sensitive to change over time and amenable to repeated measures (Bremner 1998). The CADSS will be administered by the investigator or designee with extensive professional training and experience in assessing mental illness. At Visit 1 (Screening) and Visit 2 (Baseline) the CADSS will be administered with a look-back timeframe of 1 week. At all other evaluations, the CADSS will be administered with a look-back timeframe of "since last evaluation".

### 9.4.8. Symbol Digit Coding

The Central Nervous System Vital Signs Symbol Digital Coding (SDC; Gualtieri and Johnson 2006), a version of the Symbol Digit Modalities Test (SDMT) (Smith and Jones 1982), is a variant of the Wechsler Digit Symbol Substitution Test (DSST), but the position of symbols and digits is reversed. The clinical and psychometric properties of the SDMT are similar to those of the DSST. The patient is given a training session to learn how to link numbers to digits. The test itself consists of serial presentations of screens, each of which contains a bank of 8 symbols above and 8 empty boxes below. The patient types in the number that corresponds to the symbol that is highlighted. Only the digits from 2 through 9 are used; this to avoid the confusion between

"1" and "I" on the keyboard. The test lasts for 120 seconds. The goal is to type in as many correct numbers as one can in 120 seconds.

## 9.5. Pharmacokinetics

For participants who consent to the optional PK sampling, whole blood samples of approximately 4 mL will be collected for measurement of plasma concentrations of AGN-241751 as specified in the schedule of activities (Section 2). Samples will be collected at Visit 2/2a (Day 1) at 1 hour (± 15 minutes), 2 hours (± 15 minutes), and 4 hours (± 15 minutes) post dose. At Visit 5 (Day 8), a single sample will be collected any time from 15 minutes to 3 hours post dose; site staff should record the time of the prior meal taken by the participant before the PK sample collection, whenever possible.

Instructions for the collection and handling of biological samples will be provided by the sponsor. The date and time of the administered dose of study treatment and the date and time of each sample collection will be recorded.

Samples will be used to evaluate the pharmacokinetics of AGN-241751. Each plasma sample will be divided into 2 aliquots (1 each for PK, and other analyses/backup). Samples collected for analyses of AGN-241751 plasma concentration may also be used to evaluate safety, efficacy, or exploratory biomarker aspects related to concerns arising during or after the study.

## 9.6. Pharmacodynamics

Pharmacodynamic samples are not being collected within this study.

## 9.7. Genetics

Genetics are not evaluated in this study.

## 9.8. Biomarkers

Biomarker samples are not being collected within this study.

## 9.9. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

# 10. Statistical Considerations

## 10.1. Estimands Framework

This estimand framework is being proposed for the primary and secondary endpoints.

### 10.1.1. Population

The target study population is the participants with MDD satisfying the inclusion and exclusion criteria as specified in Sections 6.1 and 6.2.

The analysis population is defined as all randomized participants who received at least 1 administration of study treatment and had a baseline MADRS total score and at least 1 postbaseline assessment for the MADRS total score during the double-blind treatment period.

### 10.1.2. Variables

The variable is the same as the primary efficacy endpoint defined in Section 10.4.1.1, which is the change from baseline in MADRS total score at 1 day after first dose of double-blind treatment; and the secondary efficacy endpoint of the change from baseline in MADRS total score at Week 3.

### 10.1.3. Intercurrent Events and Their Handling Rules

The intercurrent events involve all discontinuations of study due to any reason. Participants who discontinue study will be considered adhered to the study treatment by 1 day after the first dose for the primary endpoint and assumed adhered to the study treatment by Week 3 for the secondary endpoint.

For Day 1 primary analysis, the first dose of the study drug is administered to the participants at Baseline (Visit 2) in the clinic, and the study analysis population is defined as all randomized participants who received at least 1 administration of study treatment and had a baseline MADRS total score and at least 1 postbaseline assessment of MADRS total score. Therefore, all participants will adhere to the study treatment by Day 1.

For Week 3 secondary analysis, per the study protocol all study treatment doses including at Week 3 are administered in the clinic. Given the very short treatment period, very small (at most 5%) proportion of participants are expected not to receive the treatments at Weeks 2 or 3. Therefore assuming those discontinued treatments at Weeks 2 or 3 to adhere to study treatment will have a minimum impact on the overall analysis.

Also, this is a Phase 2 study with an important objective to inform the doses for the Phase 3 studies. Given at least 95% study participants will adhere to study treatment for the secondary endpoint and the objective of the study being dose finding, we consider a hypothetical estimand defined as all participants in the study population adhere to study treatment as an appropriate estimand.

### 10.1.4. Population-Level Summary

The population-level summary for the primary endpoint is the difference in primary variable means between each AGN-241751 dose and placebo.

Similarly, the population-level summary for the secondary endpoint is the difference in secondary variable means between each AGN-241751 dose and placebo.

## 10.2. Sample Size Determination

The sample size of approximately 50 randomized participants in each of the 5 treatment groups is not based on statistical power consideration due to the lack of information of AGN-241751 for the variability of change from baseline to 1 day after first dose in MADRS total score.

## 10.3. Populations for Analyses

The analysis populations will consist of participants as defined below:

- The modified intent-to-treat (mITT) population includes all randomized participants who received at least 1 administration of study treatment, and have a baseline MADRS total score and at least 1 postbaseline assessment for the MADRS total score during the double-blind treatment period. Participants will be summarized according to the randomized study treatment.
- The safety population includes all participants who received ≥ 1 administration of study treatment. Participants will be summarized according to the study treatment they actually received.

## 10.4. Statistical Analyses

The study statistical analysis plan (SAP) will be developed and finalized before database lock and will describe in detail the participant populations to be included in the analyses, the safety and efficacy analysis, and the procedures for accounting for missing or unscheduled data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

### 10.4.1. Efficacy Analyses

The efficacy analyses will be based on the mITT population. Baseline for efficacy is defined as the last nonmissing efficacy assessment before the first dose of study treatment. All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

For efficacy analyses in which study center is a factor, a small center will be defined as a center with fewer than 2 participants in the mITT Population. All the small centers will be pooled to form a pseudo-center. If the pseudo-center is still a small center, it will be pooled with the smallest non-small center. If there is more than one smallest non-small center, the small pseudo-center will be pooled with the smallest non-small center that has the largest center number.

#### 10.4.1.1. Primary and Secondary Endpoint

To perform the analysis based on the estimands framework, the primary and secondary efficacy endpoints are listed below and analyses will be defined in the following sections. All analyses for other efficacy endpoints listed below will be defined in the SAP.

Primary efficacy endpoint:

- Change from baseline in MADRS total score at 1 day after first dose

Secondary efficacy endpoint:

- Change from baseline in MADRS total score at Week 3

#### 10.4.1.2. Primary and Secondary Analyses

The primary analysis for the primary and secondary endpoints will be performed using an MMRM with treatment group, visit, pooled study center, and treatment group-by-visit interaction as fixed effects and the baseline value and baseline value-by-visit as covariates. An unstructured covariance matrix will be used to model the covariance of within-participant scores. If the model fails to converge based on the unstructured covariance matrix, then structures of Heterogenous Toeplitz, Toeplitz, and Compound Symmetry will be applied, in the specified order, until the model converges. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom (Kenward and Roger 1997). These analyses will be performed based on all postbaseline scores using only the OCs without imputation of missing values.

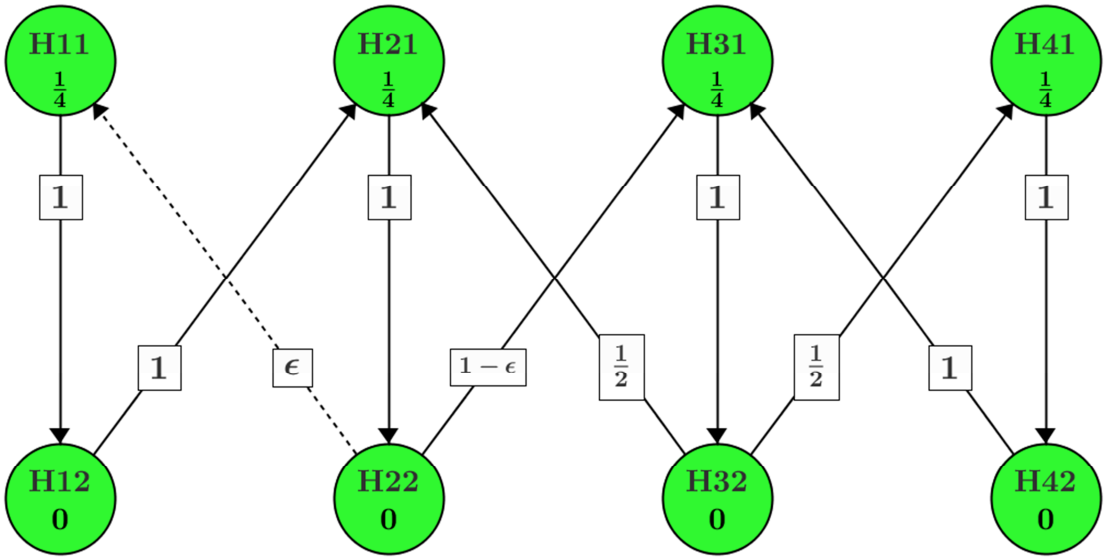
In addition, a sensitivity analysis using the multiple imputation (MI) approach under missing not at random (MNAR) assumptions will be performed on the primary and secondary efficacy parameters.

Detailed methods and procedures for the above outlined missing data-derived sensitivity analyses will be documented in the final SAP prior to the study database lock.

#### 10.4.1.3. Multiple Comparisons Procedure

Let H11, H21, H31, H41 represent the comparisons of AGN-241751 0.25 mg, 1 mg, 3 mg, and 10 mg, respectively with placebo in regarding to the primary efficacy parameter; and let H12, H22, H32, and H42 represent the comparisons of AGN-241751 0.25 mg, 1 mg, 3 mg, and 10 mg, respectively with placebo in regarding to the key secondary efficacy parameter, the graphical procedure as displayed in Figure 10-1 will be employed to controlled the overall familywise error rate (FWER) at $\alpha = 0.05$. The e in the figure represents a small positive number less than 0.0001.

**Figure 10-1 Graphical Procedure for Primary and Key Secondary Hypotheses**




### 10.4.2. Safety Analyses

The safety analysis will be performed using the safety population for the double-blind treatment period and for the safety follow-up period, if applicable, and will be fully defined in the SAP. The safety parameters will include AEs, clinical laboratory including potential Hy's law cases, vital signs, ECG, C-SSRS, BPRS+, CADSS, and SDC parameters. For each safety parameter, the last nonmissing safety assessment before the first dose of study intervention will be used as the baseline for all analyses of that safety parameter.

#### 10.4.2.1. Adverse Event

An AE will be considered a treatment-emergent adverse event (TEAE) if:

- The AE began on or after the date of the first dose of study treatment; or
- The AE was present before the date of the first dose of study treatment, but increased in severity or became serious on or after the date of the first dose of study treatment

If more than 1 AE is reported before the first dose of study treatment and is coded to the same preferred term, the AE with the greatest severity will be used as the benchmark for comparison with the AEs that were also coded to that preferred term and that occurred during the period. An AE that occurs more than 30 days after the last dose of study treatment will not be counted as a TEAE.

An AE will be considered a treatment-emergent serious adverse event (TESAE) if it is a TEAE that additionally meets any SAE criteria

The number and percentage of participants reporting TEAEs in each study treatment will be tabulated as follows:

- By system organ class and preferred term
- By system organ class, preferred term, and severity.

The number and percentage of participants reporting treatment related TEAEs in each study treatment will be tabulated by system organ class and preferred term.

If more than 1 AE is coded to the same preferred term for the same participant, the participant will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to study treatment.

Summary tables will be provided for participants with TESAEs and participants with TEAEs leading to discontinuation if 2 or more participants reported such events. Listings of all AEs, SAEs, and AEs leading to discontinuation by participant will be presented.

The definitions of an AE and SAE can be found in Appendix 4.

#### 10.4.2.2. Clinical Laboratory Assessments

Descriptive statistics of actual values and change from baseline for clinical laboratory values (in SI units) will be presented at each assessment timepoint by treatment. In addition, descriptive statistics for values and changes from the baseline values in conventional units at each assessment timepoint will be presented for selected clinical laboratory parameters listed in the SAP.

The criteria for potentially clinically significant (PCS) laboratory values will be detailed in the SAP. The number and percentage of participants who have PCS postbaseline clinical laboratory values will be tabulated by study treatment at each assessment. The percentages will be calculated relative to the number of participants who have available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with available non-PCS baseline values and at least 1 PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided.

#### 10.4.2.3. Vital Signs

Descriptive statistics of actual values and change from baseline for vital signs (systolic and diastolic BP, pulse rate, weight, and temperature) will be presented at each assessment timepoint by treatment.

Vital sign values will be considered to be PCS if they meet both the observed value criterion and the change from baseline value criterion that will be detailed in the SAP. The number and percentage of participants who have PCS postbaseline vital sign values will be tabulated by study treatment for each assessment. The percentages will be calculated relative to the number of participants who have available baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided.

#### 10.4.2.4. Electrocardiograms

Descriptive statistics of actual values and change from baseline for ECG parameters (ie, heart rate, PR interval, QRS interval, QT interval, and QTc interval) will be presented at each assessment timepoint by treatment.

The number and percentage of participants with PCS postbaseline values will be tabulated by study treatment. The criteria for PCS ECG values will be detailed in the SAP. The percentages will be calculated relative to the number of participants with an available non-PCS baseline value and at least one postbaseline assessment. The numerator will be the total number of participants with an available non-PCS baseline value and at least one PCS postbaseline ECG value. A supportive listing of participants with PCS postbaseline values will be provided and will include the participant number and the baseline and postbaseline values. A listing of all AEs for participants with PCS ECG values will also be provided.

A shift table from baseline to the end of study in the investigator's overall interpretation of the ECG will be presented by treatment group for the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant. A tabular display of participants with postbaseline clinically significant ECG abnormalities according to the investigator's overall interpretation will be provided.

The number and percentage of participants with a change from baseline QTc > 30 msec but not exceeding 60 msec and of participants with an increase > 60 msec will be tabulated by treatment group. A supportive listing that includes the participant identification number, all QTc values (including change from baseline values), and all AEs will be provided for all participants who have postbaseline QTc changes > 30 msec.

#### 10.4.2.5. Other Safety Parameters

Other safety parameters include the BPRS+, CADSS, C-SSRS, and SDC.

Descriptive statistics of actual values and change from baseline for BPRS+ total score will be presented at each assessment timepoint by treatment.

Descriptive statistics of actual values and change from baseline for CADSS total score will be presented at each assessment timepoint by treatment. The CADSS total score is defined as the sum of scores for 23 subjective items.

The number and percentage of participants with suicidal ideation or suicidal behavior as recorded on the C-SSRS will be summarized by treatment. The distribution of responses for most severe suicidal ideation and most severe suicidal behavior during the participant's lifetime, during the double-blind treatment period, and during the safety follow-up period will also be presented by treatment. Supportive listings will be provided and will include the participant number, lifetime history, and postbaseline values. Intensity of suicidal ideation, suicidal behavior type, and lethality of suicidal behavior will also be included in these listings. A listing of all AEs occurring in participants who have suicidal ideation or suicidal behavior will also be provided.

Descriptive statistics will be presented at each assessment timepoint by treatment for the SDC parameters including the number of symbols completed, the rate of completion (number of

symbols completed/time of trial), the number of corrected responses (symbols completed correctly), and the number of errors (symbols completed incorrectly).

### 10.4.3. Interim Analyses

No interim analysis planned.

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# 12. Appendices

## 12.1. Appendix 1: Abbreviations and Trademarks

| | |
|---|---|
| ADT | antidepressant therapy |
| AE | adverse event |
| ALT | alanine aminotransferase |
| AESI | adverse event of special interest |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| BMI | body mass index |
| BPRS+ | Brief Psychiatric Rating Scale - Positive Symptoms Subscale |
| CADSS | Clinician Administered Dissociative States Scale |
| CFR | Code of Federal Regulations |
| CGI-S | Clinical Global Impressions-Severity |
| $C_{max}$ | maximum concentration |
| CNS | central nervous system |
| CSF | cerebrospinal fluid |
| C–SSRS | Columbia–Suicide Severity Rating Scale |
| C-VISA | Clinical Validation Inventory for Study Admission |
| DALY | disability adjusted life years |
| DSM-5 | *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition |
| DSST | Digit Symbol Substitution Test |
| DxV | Diagnostic Validation |
| ECT | electroconvulsive therapy |
| ECG | electrocardiogram, electrocardiographic |
| eCRF | electronic case report form |
| ET | early termination |
| FDA | Food and Drug Administration |
| FSH | follicle stimulating hormone |
| GCP | good clinical practice |
| β-hCG | β-human chorionic gonadotropin |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | human immunodeficiency virus |
| HRT | hormonal replacement therapy |
| ICF | informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IEC | independent ethics committee |

| | |
|---|---|
| IRB | Institutional Review Board |
| ITT | Intent-to-Treat |
| IWRS | Interactive Web Response System |
| LTP | long-term potentiation |
| MADRS | Montgomery- Åsberg Depression Rating Scale |
| MDD | major depressive disorder |
| mITT | modified intent-to-treat |
| MI | multiple imputation |
| MMRM | mixed-effect model for repeated measures |
| MNAR | missing not at random |
| NMDA | N-methyl-D-aspartate |
| NMDAR | N-methyl-D-aspartate receptor |
| NOAEL | no-observed-adverse-effect level |
| PCS | potentially clinically significant |
| QTc | QT interval corrected for heart rate |
| QTcB | QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/[RR]^{1/2}$) |
| QTcF | QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/[RR]^{1/3}$) |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SCID | Structured Clinical Interview for DSM disorders |
| SDC | Symbol Digit Coding |
| SDMT | Symbol Digit Modalities Test |
| SNRI | selective serotonin and norepinephrine reuptake inhibitor |
| SSRI | selective serotonin reuptake inhibitor |
| TEAE | treatment-emergent adverse event |
| TESAE | treatment-emergent serious adverse event |
| $T_{max}$ | time to reach maximum concentration |
| UDS | urine drug screen |
| ULN | upper limit of normal |
| WOCBP | woman of childbearing potential |

## 12.2. Appendix 2: Clinical Laboratory Tests

Blood and urine samples for clinical laboratory tests will be collected as listed in the schedule of activities (Section 2).

A central laboratory will be used to evaluate all urine and blood samples, which will be collected, processed, and stored according to the instructions provided by the laboratory

During screening, the investigator will assess the clinical significance of any values that are outside the reference ranges provided by the central laboratory; participants with abnormalities judged to be clinically significant will be excluded from the study.

Participants will be asked to fast overnight or for at least 8 hours before arriving at the study center for appointments involving the collection of clinical laboratory blood tests.

The following clinical laboratory levels will be measured at Visit 1 (Screening) only:

| | |
|---|---|
| **Clinical laboratory screening tests:** | Hemoglobin A1c (HbA1c), fasting insulin, thyroid-stimulating hormone (TSH), triiodothyronine (T3), and free thyroxine (free T4) |
| **Hepatitis screening:** | Hepatitis–C virus antibody, hepatitis–B surface antigen, and hepatitis-B core antibody total will be tested. Reflex hepatitis-B core antibody IgM will be performed for all hepatitis–B core antibody total positive or reactive results. Positive test results will be sent for confirmation testing. |

The following clinical laboratory levels will be measured at Visit 1 (Screening) and Visit 9/ET:

| | |
|---|---|
| **Hematology:** | Absolute and differential white blood cell count, erythrocyte count, hemoglobin, hematocrit, platelet count, and red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration) |
| **Chemistry:** | Sodium, potassium, calcium, chloride, bicarbonate, magnesium, gamma glutamyl transferase, phosphate, glucose, blood urea nitrogen, creatinine, creatine phosphokinase, total protein, alkaline phosphatase, albumin, bilirubin (total; direct; indirect), ALT, AST, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides |
| **Urinalysis:** | Specific gravity, pH, protein, glucose, ketones, and blood |
| **UDS:** | Benzoylecgonine (cocaine), barbiturates, amphetamines, benzodiazepines, cannabinoids, opiates, methadone, phencyclidine |
| **Pregnancy screening and Visit 9/ET:** | Serum β-hCG |

Clinical laboratory tests may be performed under special circumstances (and at investigator's discretion).

A negative UDS for cocaine, phencyclidine, barbiturates, and methadone is required at Visit 1 (Screening) for the participant to continue in the study. Participants with a positive screening UDS for opiates (other than methadone), cannabinoids, or episodic use of benzodiazepines may continue in the study provided the drug was prescribed for a legitimate medical purpose and can be discontinued prior to study participation and a repeat UDS is negative for these substances prior to enrollment. An exception is made for episodic use of benzodiazepines, which may be continued as described in Section 7.7.2.

A UDS may be performed at any time during the study at the discretion of the investigator. A participant with a positive UDS for benzodiazepines or opiates at any postrandomization visit may be allowed to continue in the study provided the participant has been prescribed the medication and it is being used for legitimate medical purpose in the investigator's judgment.

Serum pregnancy tests will be conducted at Visit 1 (Screening) and Visit 9/ET as specified in the schedule of activities (Section 2) and at investigator's discretion at any time during the study. Positive results on the pregnancy test at Visit 1 (Screening) will exclude participants from participating in the study. Investigators should inquire at every study visit about the continued use of acceptable methods of contraception in women of childbearing potential. If there is any question of noncompliance with contraception or if there is any reason to suspect pregnancy, the following should be performed:

- Urine pregnancy test
    - If the urine pregnancy test is positive, the participant must be discontinued from the study immediately
    - If the urine pregnancy test is negative, a serum β-hCG pregnancy test must be performed for confirmation.

Positive pregnancy test results during the study will result in participant termination from the study.

Other laboratory assessments may be repeated at any visit if there was an abnormal finding at the most recent previous evaluation or if additional information is clinically necessary to appropriately evaluate the participant's current condition, follow up, and/or manage an adverse experience.

## 12.3. Appendix 3: Study Governance Considerations

**Regulatory and Ethical Considerations**

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the overall conduct of the study at the site and adherence to requirements of applicable local regulations, for example 21 CFR, ICH guidelines, the IRB/IEC, and European regulation 536/2014 for clinical studies (if applicable)

**Financial Disclosure**

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

**Informed Consent Process**

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

**Data Protection**

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

**Publication Policy**

- Allergan as the sponsor has proprietary interest in this study. An integrated clinical and statistical report will be prepared at the completion of the study.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements and will follow the sponsor's standard operating procedure on publications.

**Data Quality Assurance**

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period or otherwise notified in writing by the sponsor. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

**Source Documents**

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

**Study and Site Closure**

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

## 12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

**Definition of AE**

| AE Definition |
|---|
| • An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment.<br>• NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.<br>**AE of Special Interest (AESI)**<br>An adverse event of special interest (serious or nonserious) is one of scientific and medical concern specific to the sponsor's study drug/device or program, which warrants ongoing monitoring and rapid communication by the investigator to the sponsor. Such an event might warrant further investigation in order to characterize and understand it.<br>Nonserious AESIs should be reported to the sponsor within 72 hours and serious AESIs should be reported to the sponsor within 24 hours.<br>• The AESI should be reported to the SAE reporting fax number (provided on the title page of this protocol).<br>• The Adverse Event of Special Interest form, along with a targeted questionnaire, if applicable, should be used for reporting the AESI, even if a serious outcome may not apply. |

| **Events Meeting the AE Definition** |
|---|
| • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease)<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition<br>• New condition detected or diagnosed after study treatment administration even though it may have been present before the start of the study<br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction<br>• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such intentional overdoses should be reported regardless of sequelae.<br>• Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AEs or SAEs if they fulfil the definition of an AE or SAE. |

| **Events NOT Meeting the AE Definition** |
|---|
| • Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition<br>• The disease/disorder being studied or expected progression, signs, or symptoms (clearly defined) of the disease/disorder being studied, unless more severe than expected for the participant's condition<br>• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE<br>• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)<br>• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen |

**Definition of SAE**

SAEs must meet both the AE criteria described above and the seriousness criteria listed below.

| **An SAE is defined as any untoward medical occurrence that, at any dose:** |
|---|
| **a. Results in death** |
| **b. Is life threatening**<br>The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. |
| **c. Requires inpatient hospitalization or prolongation of existing hospitalization**<br>In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.<br>Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. |
| **d. Results in persistent disability/incapacity**<br>• The term disability means a substantial disruption of a person's ability to conduct normal life functions.<br>• This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption. |
| **e. Is a congenital anomaly/birth defect** |
| **f. Other situations:**<br>• Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.<br>Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. |

**Recording an AE and/or SAE**

**AE and SAE Recording**

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

**Assessment of Intensity**

| | |
|---|---|
| MILD | A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. |
| MODERATE | A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. |
| SEVERE | A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. |

An event is defined as *serious* when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

**Assessment of Causality**

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**Reporting of SAEs**

**SAE Reporting to the Sponsor via Fax or Email**

- Facsimile transmission is the preferred method to transmit SAE information. The fax number is +1-714-796-9504 (backup number is +1-714-246-5295).
- Email of the SAE information is also acceptable. The email address is IR-Clinical-SAE@allergan.com.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE form, sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE form within the designated reporting time frames.
- Contacts for SAE reporting can be found on the protocol title page.

## 12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

**Definitions**

**Woman of Childbearing Potential (WOCBP)**

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

**Women in the following categories are not considered WOCBP**

1. Premenarchal
2. Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the acceptable non-hormonal contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

**Contraception Guidance**

**Male Participants**

- Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the study:
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
  - Vasectomy

- Female partners of male study subjects reliably use one of the following;
  - Hormonal contraceptives (ie, oral, patch, injection, implant)
  - Vaginal contraceptive ring
  - Intrauterine device
  - Bilateral tubal ligation
  - Essure placement with correct placement verified by hysterosalpingogram
  - Surgical sterilization
  - Male or female condom with spermicide
  - Cap, diaphragm, or sponge with spermicide

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the study.
- Refrain from donating sperm for the duration of the study and for 10 weeks following the end of study.
- Refrain from attempting pregnancy with female for 10 weeks following the end of study.

**Female Participants**

Female participants of childbearing potential are eligible to participate if they agree to use an acceptable method of contraception consistently and correctly, as listed below.

- Hormonal contraceptives (ie, oral, patch, injection, implant)
- Vaginal contraceptive ring
- Intrauterine device
- Bilateral tubal ligation
- Essure placement with correct placement verified by hysterosalpingogram
- Surgical sterilization (bilateral tubal ligation)
- Male or female condom with spermicide
- Cap, diaphragm, or sponge with spermicide
- Abstinence (as described above)
- Male partner has vasectomy

Refrain from attempting pregnancy for 4 – 5 weeks following the end of study.

**Pregnancy Testing**

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
- Additional pregnancy testing during the treatment period can be performed any time at the Investigator's discretion and after the last dose of study treatment.

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected

**Collection of Pregnancy Information**

**Male Participants with Partners Who Become Pregnant**

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

**Female Participants Who Become Pregnant**

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy related SAE considered reasonably related to the study treatment by the investigator will be reported to the sponsor as described in Section 9.2. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

## 12.6. Appendix 6: Concomitant Medications

Therapy considered necessary for the participant's welfare may be given at the discretion of the investigator. If the permissibility of a specific medication/treatment is in question, please contact the sponsor.

***Medications Allowed (Y) and Medications Not Allowed (N) as Concomitant Medications***

| ***Drug Class*** | ***Frequency of Use*** | | ***Restrictions/Exceptions/Clarifications*** |
|---|---|---|---|
| | ***Episodic (PRN)*** | ***Chronic*** | |
| Attention deficit hyperactivity disorder medications/stimulants | N | N | |
| Analgesics | Y | Y | Nonnarcotic analgesics are allowed. Pregabalin and indomethacin are not allowed. Medically appropriate episodic use of narcotic analgesics including tramadol for acute medical indications limited to 3 days for an episode is allowed. |
| Anesthetics - general | N | N | If procedures requiring general anesthesia are to occur/have occurred, please contact the Study Physician to report the medical condition(s). |
| Anesthetics - local | Y | N | Topical anesthetics for venipuncture (eg, EMLA cream) are allowed. |
| Anorectics | N | N | |
| Antacids | Y | Y | |
| Antiacne agents | Y | Y | Topical agents only, including topical antibiotics. Isotretinoin (Accutane) is not allowed. |
| Antianginal agents | Y | Y | |
| Antiarrhythmics | N | Y | Only class II agents (eg, esmolol), class IV agents (eg, diltiazem, verapamil), and digoxin are allowed. Dosage must be stable for 1 month before screening. For participants on digoxin, there should be a digoxin level obtained within 2 months prior to screening. Adenosine, parasympatholytics (atropine), and sympathomimetics (epinephrine, dopamine) are not allowed. ***Propranolol (Inderal) is not allowed.*** |
| Anti-asthma agents | Y | Y | Systemic corticosteroids are not allowed. Inhaled steroids at approved dosages are allowed. |
| Antibiotics | Y | Y | |
| Anticoagulants | N | N | Please see under antiplatelet below. |
| Anticonvulsants | N | N | |
| Antidepressants | N | N | |
| Antidiarrheal preparations | Y | N | Only Imodium (loperamide HCl), Pepto-Bismol, and kaolin preparations are allowed. |

***Medications Allowed (Y) and Medications Not Allowed (N) as Concomitant Medications***

| ***Drug Class*** | ***Frequency of Use*** | | ***Restrictions/Exceptions/Clarifications*** |
|---|---|---|---|
| | ***Episodic (PRN)*** | ***Chronic*** | |
| Antifungal agents<br>Systemic<br>Topical | <br>N<br>Y | <br>N<br>Y | |
| Antihistamines | Y | Y | Sedating antihistamines are not allowed. Only fexofenadine (Allegra), loratadine (Claritin), desloratadine (Clarinex), cetirizine (Zyrtec), and levcetirizine (Xyzal) are allowed for episodic or chronic use. Terfenadine is not allowed. See Cough and Cold Preparations for combination products. |
| Antihypertensives | N | Y | Reserpine (Diupres), clonidine (Catapres), guanabenz (Wytensin), guanfacine (Tenex and Intuniv), guanethidine (Ismelin), methyldopa (Aldomet), direct vasodilators (hydralazine, minoxidil), nitroglycerin, sodium nitroprusside, and diazoxide are not allowed. Propranolol (Inderal) is not allowed. For all others (α1-blockers, β-blockers, calcium channel blockers, ACE inhibitors, etc), the medication and dosage should be stable for 1 month before Screening (for diuretics, the participant should have been treated with the diuretic for at least 3 months, with at least 1 month on the current dose). |
| Anti-inflammatory drugs | Y | Y | Chronic use is allowed if dosage is stable for 1 month prior to Screening. Indomethacin (Indocin) and systemic corticosteroids are not allowed. |
| Antinauseants/antiemetics | Y | N | Antidopaminergic agents (such as metoclopramide, domperidone, and phenothiazines), scopolamine, 5-HT3 receptor antagonists (eg, ondansetron) and sedating (H1) antihistamines are **not** allowed. Phosphoric acid preparations (Emetrol, Emecheck), bismuth subsalicylate (Pepto-Bismol), and cola syrup are allowed. |
| Antineoplastics | N | N | |
| Antiobesity agents/appetite suppressants | N | N | Over-the-counter Alli (Xenical) is not allowed. Sibutramine (Meridia), phenylpropanolamine, and phentermine (Adipex-P, others) are not allowed. |
| Antiplatelet agents | N | Y | Aspirin (maximum dosage of 325 mg/day) and clopidogrel (Plavix) are allowed. Medication dosage must be stable for 1 month prior to screening. |

***Medications Allowed (Y) and Medications Not Allowed (N) as Concomitant Medications***

| ***Drug Class*** | ***Frequency of Use*** | | ***Restrictions/Exceptions/Clarifications*** |
|---|---|---|---|
| | ***Episodic (PRN)*** | ***Chronic*** | |
| Antipsoriatic treatments | Y | Y | Only topical treatments are allowed (vitamin D analogs, anthralin, topical retinoids); 1 month stability is required. Oral medications, such as oral retinoids (eg acitretin), methotrexate, azathiaprine, cycloprorin, and immunomodulator drugs are **not** allowed. |
| Antipsychotics | N | N | |
| Antismoking medications | N | N | Varenicline (Chantix) and bupropion (Zyban) are not allowed. However, nicotine replacement therapies are allowed. |
| Antiviral agents | Y | Y | Only oral or topical agents are allowed. Acyclovir, famciclovir, valacyclovir, penciclovir, docosanal, trifluridine, and vidarabine are allowed.<br>Interferons are not allowed.<br>Anti-HIV drugs are not allowed.<br>Contact the medical monitor if participant is taking anti-Hepatitis C medications. |
| Anxiolytics | Y | N | Episodic use of benzodiazepines up to approximately 2 mg/day lorazepam equivalent dose and for up to 3 consecutive days at a time can be given for anxiety-related conditions and agitation (not permitted within 8 hours of efficacy assessments). |
| Cough and cold preparations | Y | N | Cough/cold preparations containing dextromethorphan or narcotics are not allowed. Decongestant preparations containing pseudoephedrine or phenylpropanolamine are not allowed. Phenylephrine nasal sprays are allowed for brief medically appropriate use, for up to 5 days. Combination products containing the word “Nighttime” or some synonym routinely include a sedating antihistamine are not allowed. Combination products ending in “D” routinely contain a stimulant such as pseudoephedrine or phenylpropanolamine and are not allowed (also see Antihistamines). |
| $H_2$ blockers/proton pump inhibitors/prokinetic agents | Y | Y | Tagamet (cimetidine) is not allowed.<br>Metoclopramide and cisapride are **not** allowed. |
| Hormones (nonreproductive) | N | Y | Thyroid hormone replacement is allowed. Therapeutic use in psychiatric disorders (eg, T3 augmentation therapy) is **not** allowed. Dosage of thyroid medication must be stable for 1 month prior to screening. |

***Medications Allowed (Y) and Medications Not Allowed (N) as Concomitant Medications***

| ***Drug Class*** | ***Frequency of Use*** | | ***Restrictions/Exceptions/Clarifications*** |
|---|---|---|---|
| | ***Episodic (PRN)*** | ***Chronic*** | |
| Hormones (reproductive) | Y | Y | Hormonal contraception such as oral contraceptives (estrogen-progestin combination or progestin alone), transdermally delivered contraceptives (eg, Ortho Evra), depot injections (eg, Depo-Provera), vaginal contraceptive ring (eg, NuvaRing), and contraceptive implant (eg, Implanon, Norplant) are allowed. Must follow package inserts for hormonal contraception, regarding time must be taking same before they are effective (eg, often 1 cycle). Refer to Section 12.5 for specifics of allowed contraception. |
| Hormone suppressants | N | Y | Only Proscar (finasteride) and Avodart (dutasteride) are allowed. Dosage must be stable for 1 month prior to screening. |
| Hypoglycemic agents | N | Y | Oral hypoglycemic agents are allowed, except pioglitazone and troglitazone are not allowed. Chronic use of insulin is allowed. Dosage must be stable for 1 month prior to screening. |
| Hypolipidemics | N | Y | Niacin and niacinamide are allowed if dosage has been stable for 3 months prior to screening. Statins (lovastatin, pravastatin, simvastatin, atorvastatin, fluvastatin, rosuvastatin), fibrates (gemfibrozil, fenofibrate), and ezetimibe are allowed. Dosage must be stable for 1 month prior to screening. Bile sequestrants are not allowed. |
| Laxatives | Y | Y | Episodic and chronic use of bulk laxatives and emollient laxatives are allowed. Episodic use of stimulant laxatives containing senna, bisacodyl, and anthraquinone derivatives is allowed. Episodic use of osmotic laxatives such as oral magnesium hydroxide (milk of magnesia), oral sodium citrate, and sodium biphosphate is allowed. Hyperosmotic laxatives such as sorbitol, lactulose, and polyethylene glycol are not allowed. |
| Migraine medications | Y | N | Triptans should be used with some caution. Note that cases of serotonin syndrome have been reported with the concomitant use of triptans and serotonergic reuptake inhibitors. Ergotamine or ergot derivatives are not allowed. |
| Muscle relaxants | N | N | |

***Medications Allowed (Y) and Medications Not Allowed (N) as Concomitant Medications***

| ***Drug Class*** | ***Frequency of Use*** | | ***Restrictions/Exceptions/Clarifications*** |
|---|---|---|---|
| | ***Episodic (PRN)*** | ***Chronic*** | |
| Psychotropic drugs not otherwise specified (including herbal products) | N | N | No drugs with psychomotor effects or with anxiolytic, antidepressant, stimulant, antipsychotic, or sedative properties are allowed except as stipulated by the protocol. Herbal/dietary products and supplements with potential psychoactive actions, including St. John's wort, ginkgo biloba, kava, SAMe, valerian root, DHEA, tyrosine, tryptophan and 5-HTP are not allowed. Omega-3 supplements are allowed if the dose of EPA is ≤ 1000 mg/day, and the participant has been taking same for at least 1 month. |
| Sedatives/hypnotics | Y | N | Only zolpidem (Ambien up to 10 mg/day and Ambien CR up to 12.5 mg/day), zaleplon (Sonata) up to 20 mg/day, eszopiclone (Lunesta) up to 7.5 mg/day, zopiclone up to 7.5 mg/day, and suvorexant (Belsomra) up to 10 mg/day are permitted, up to 3 times a week, if required for sleep. Sedatives/hypnotics may not be used in the 8 hours before any behavioral assessments. |
| Steroids, inhalant | Y | Y | |
| Steroids, intra-articular | Y | N | |
| Steroids, systemic | N | N | |
| Steroids, topical | Y | Y | |
| Vaccines | Y | N | |

N = not allowed; PRN = as needed; Y = yes, allowed.

## 12.7. Appendix 7: Standard Discontinuation Criteria

| CDISC Submission Value | CDISC Definition |
|---|---|
| Adverse event | Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. For further information, see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. [Modified from ICH E2A] Synonyms: side effect, adverse experience. See also serious adverse event, serious adverse experience. (CDISC glossary) |
| Completed | To possess every necessary or normal part or component or step; having come or been brought to a conclusion (NCI) |
| Lack of efficacy | The lack of expected or desired effect related to a therapy (NCI) |
| Lost to follow-up | The loss or lack of continuation of a subject to follow-up |
| Non-compliance with study drug | An indication that a subject has not agreed with or followed the instructions related to the study medication (NCI) |
| Other | Different than the one(s) previously specified or mentioned (NCI) |
| Pregnancy | Pregnancy is the state or condition of having a developing embryo or fetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth. (NCI) |
| Protocol deviation | An event or decision that stands in contrast to the guidelines set out by the protocol (NCI) |
| Screen failure | The potential subject who does not meet one or more criteria required for participation in a trial |
| Site terminated by sponsor | An indication that a clinical study was stopped at a particular site by its sponsor (NCI) |
| Study terminated by sponsor | An indication that a clinical study was stopped by its sponsor (NCI) |
| Withdrawal by subject | An indication that a study participant has removed itself from the study (NCI) |

## 12.8. Appendix 8: Montgomery-Åsberg Depression Rating Scale

1. **APPARENT SADNESS**—Representing despondency, gloom and despair (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   0 No sadness.
   1
   2 Looks dispirited but does brighten up without difficulty.
   3
   4 Appears sad and unhappy most of the time.
   5
   6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS—**Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.

   0 Occasional sadness in keeping with the circumstances.
   1
   2 Sad or low but brightens up without difficulty.
   3
   4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   5
   6 Continuous or unvarying sadness, misery or despondency.

3 **INNER TENSION**—Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   0 Placid. Only fleeting inner tension.
   1
   2 Occasional feelings of edginess and ill-defined discomfort.
   3
   4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   5
   6 Unrelenting dread or anguish. Overwhelming panic.

4. **REDUCED SLEEP**—Representing the experience of reduced duration or depth of sleep compared to the patient's own normal pattern when well.

   0 Sleeps as usual.
   1
   2 Slight difficulty dropping off to sleep or slightly reduced, light, or fitful sleep.
   3
   4 Sleep reduced or broken by at least 2 hours.
   5
   6 Less than 2or 3 hours sleep.

5. **REDUCED APPETITE**—Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

   0 Normal or increased appetite.
   1
   2 Slightly reduced appetite.
   3
   4 No appetite. Food is tasteless.
   5
   6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**—Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.

   0 No difficulties in concentrating.
   1
   2 Occasional difficulties in collecting one's thoughts.
   3
   4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
   5
   6 Unable to read or converse without great difficulty.

7. **LASSITUDE**—Representing a difficulty getting started or slowness initiating and performing everyday activities.

   0 Hardly any difficulty getting started. No sluggishness.
   1
   2 Difficulties in starting activities.
   3
   4 Difficulties in starting simple routine activities which are carried out with effort.
   5
   6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**—Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

   0 Normal interest in the surroundings and in other people.
   1
   2 Reduced ability to enjoy usual interests.
   3
   4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
   5
   6 The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives or friends.

9. **PESSIMISTIC THOUGHTS**—Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.

   0 No pessimistic thoughts.
   1
   2 Fluctuating ideas of failure, self-reproach or self-deprecation.
   3
   4 Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
   5
   6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

**10. SUICIDAL THOUGHTS**—Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

0 Enjoys life or takes it as it comes.

1

2 Weary of life. Only fleeting suicidal thoughts.

3

4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.

5

6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

## 12.9. Appendix 9: Clinical Global Impressions–Severity

**SEVERITY OF ILLNESS**

Considering your total clinical experience with this population, how mentally ill is the patient at this time? (Check one)

1 Normal, not at all ill

2 Borderline ill

3 Mildly ill

4 Moderately ill

5 Markedly ill

6 Severely ill

7 Among the most extremely ill patients

## 12.10. Appendix 10: Brief Psychiatric Rating Scale – Positive Symptoms Subscale

**4-Item Positive Symptom Rating Scale***

NA = not able to be assessed, 1 = symptom not present, 6/7 = severe/extremely severe

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1. Suspiciousness | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 2. Unusual Thought Content | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 3. Hallucinations | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 4. Conceptual Disorganization | NA | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

**SCORE: _____**

## 12.11. Appendix 11: Clinician Administered Dissociative States Scale

**The Clinician Administered Dissociative States Scale (CADSS)**

J. Douglas Bremner, Carolyn Mazure, Frank W. Putnam

Name_____ ID_____ Date_____

**Subjective Items:**

1. Do things seem to be moving in slow motion?
   - 0= Not at all.
   - 1= Mild, things seem slightly slowed down, but not very noticeable.
   - 2= Moderate, things are moving about twice as slow as normally.
   - 3= Severe, things are moving so slowly that they are barely moving.
   - 4= Extreme, things are moving so slowly, I have the perception that everything has come to a stop, as if time is standing still.
2. Do things seem to be unreal to you, as if you are in a dream?
   - 0= Not at all.
   - 1= Mild, things seem a little unreal, but I'm well aware of where I'm at.
   - 2= Moderate, things seem dreamlike, although I know I am awake.
   - 3= Severe, things seem very dreamlike, although I know that I am here, I have the feeling like I might be asleep.
   - 4= Extreme, I feel like nothing is real, like I should pinch myself to wake up, or ask someone if this is a dream.
3. Do you have some experience that separates you from what is happening; for instance, do you feel as if you are in a movie or a play, or as if you are a robot?
   - 0= Not at all.
   - 1= Mild, I feel a little bit separated from what is happening, but I am basically here.
   - 2= Moderate, I feel somewhat separated from what is going on, or I feel as if I am in a movie or a play.
   - 3= Severe, I feel extremely separated from what is happening, but I can understand what people are saying.
   - 4= Extreme, I feel as if everyone around me is talking a foreign language, so that I cannot understand what they are saying, or I feel as if I am on the outside looking in, or like I am a robot or a machine.
4. Do you feel as if you are looking at things from outside of your body?
   - 0= Not at all.
   - 1= Mild, I feel somewhat disconnected from myself, but I am basically all together.
   - 2= Moderate, I feel like I am just outside of my body, but not looking down upon myself from far above.
   - 3= Severe, I feel like I am twenty feet or more away from my body, looking down from above.
   - 4= Extreme, I feel as if I am hundreds of feet above myself, looking down at myself and everyone else here.
5. Do you feel as if you are watching the situation as an observer or a spectator?
   - 0= Not at all.
   - 1= Mild, I feel slightly detached from what is going on, but I am basically here.
   - 2= Moderate, I feel somewhat removed as an observer or a spectator, but I am definitely in this room.
   - 3= Severe, I feel very much as if I am an observer or a spectator, but I am still here in

this room.

4= Extreme, I feel completely removed from what is happening, as if I am not a part of this experience in any way, but totally removed from what is happening, as an observer or a spectator.

6. Do you feel disconnected from your own body?
   0= Not at all.
   1= Mild, I feel a little bit disconnected from myself, but I am basically all here.
   2= Moderate, I feel somewhat detached from my own body, but I am basically all together.
   3= Severe, I feel detached from my own body, but not far removed from my body, and I feel as if it is me there.
   4= Extreme, I feel like I am completely out of my body, as if I am looking at my own body from a long way off, as if there is another person there.
7. Does your sense of your own body feel changed: for instance, does your own body feel unusually large or unusually small?
   0= Not at all.
   1= Mild, I have a vague feeling that something about my body has changed, but I can't say exactly what it is.
   2= Moderate, I feel like my body has increased or decreased in size slightly, or that it feels somewhat as if it is not my body.
   3= Severe, I feel as if my body has increased to twice its normal size, or decreased to twice its normal size, or I very much feel as if this is not my body.
   4= Extreme, I feel as if my body has swelled up to at least ten times its normal size, or as if it is ten times as small, or as if my arms have become like toothpicks.
8. Do people seem motionless, dead, or mechanical?
   0= Not at all.
   1= Mild, people seem a little bit more motionless, dead, or mechanical than would be normal.
   2= Moderate, people seem to be at least twice as motionless or mechanical than would be normal.
   3= Severe, people seem to be barely moving, or barely alive, or very mechanical.
   4= Extreme, it's as if everyone were frozen or completely like machines.
9. Do objects look different than you would expect?
   0= Not at all.
   1= Mild, things seem slightly different than normal, although it is barely perceptible.
   2= Moderate, things are somewhat distorted, but I have no problems recognizing things around me.
   3= Severe, things are much more distorted or unreal than normal, but I am able to recognize things in the room.
   4= Extreme, like everything is distorted, not real, I feel like I cannot recognize anything, everything is alien or strange.
10. Do colors seem to be diminished in intensity?
   0= Not at all.
   1= Mild, things seem slightly paler than usual if I think about it.
   2= Moderate, colors are somewhat diminished, but still recognizable.
   3= Severe, colors are extremely pale, in no way as vivid as they usually are.

4= Extreme, as if everything is in black and white, or all the colors have been washed out.

11. Do you see things as if you were in a tunnel, or looking through a wide angle photographic lens?
    0= Not at all.
    1= Mild, I feel a little bit like I am looking through a tunnel, or a wide angle lens.
    2= Moderate, the periphery of my vision is blacked out, but I still have most of my visual field, or things are somewhat like a wide angle lens.
    3= Severe, it seems as if I'm looking through a tunnel, or through a wide angle lens, but I can see everything clearly.
    4= Extreme, as if I'm looking through a pair of binoculars backwards, where everything around the periphery is blacked out, and I can see a little point of light at the end of a tunnel, with little tiny people and objects, or I am seeing things as if through a wide lens and things are incredibly expanded.
12. Does this interview [assessment, questionnaire] seem to be taking much longer than you would have expected?
    0= Not at all.
    1= Mild, it seems as if this interview has gone on for at least twice as long as the true elapsed time.
    2= Moderate, it seems as if this interview has gone on for at least two hours.
    3= Severe, it seems as if at least ten hours have gone on since the start of the interview.
    4= Extreme, it seems as if time is standing still, so that we have been here at this point in time forever.
13. Do things seem to be happening very quickly, as if there is a lifetime in a moment?
    0= Not at all.
    1= Mild, things are happening slightly faster than normal.
    2= Moderate, things seem to be happening at least twice as fast as normal.
    3= Severe, things seem to be happening at least 10 times faster than normal.
    4= Extreme, as if this whole experience has happened at once, or as if there is a lifetime in a moment.
14. Have there been things which have happened during this interview [assessment] that now you can't account for?
    0= Not at all.
    1= Mild, there may have been things which happened which now I can't account for, but nothing pronounced.
    2= Moderate, at least once there were things which happened which now I can't account for.
    3= Severe, at least twice I have lost several minutes of time, so that now there are things I cannot account for.
    4= Extreme, large pieces of time are missing, of ten minutes or more, so that I am confused about what has happened.
15. Have you spaced out, or in some other way lost track of what was going on during this experience?
    0= Not at all.
    1= Mild, I have had some episodes of losing track of what is going on, but I have

followed everything for the most part.
2= Moderate, I have lost at least a minute of time, or have completely lost track of what is going on now.
3= Severe, I have lost several segments of time of one minute or more.
4= Extreme, I have lost large segments of time of at least 15 minutes or more.

16. Have sounds almost disappeared or become much stronger than you would have expected?
0= Not at all.
1= Mild, things are either a little quieter than normal, or a little louder than normal, but it is not very noticeable.
2= Moderate, things have become about twice as soft as normal, or twice as loud as normal.
3= Severe, things have become very quiet, as if everyone is whispering, or things have become very loud (although not deafening).
4= Extreme, things have become completely silent, or sounds are so loud that it is deafening, and I feel as if I am going to break my eardrums.

17. Do things seem very real, as if there is a special sense of clarity?
0= Not at all.
1= Mild, things seem to be a little bit more real than normal.
2= Moderate, things seem to be more real than normal.
3= Severe, things seem to be very real or have a special sense of clarity.
4= Extreme, things seem to have an incredible sense of realness or clarity.

18. Does it seem as if you are looking at the world through a fog, so that people and objects appear far away or unclear?
0= Not at all.
1= Mild, things seem somewhat foggy and unclear, or I do have the feeling that things are far away, but there is not a major effect on how I perceive things around me.
2= Moderate, things seem very foggy and unclear, or things seem like they are far away, but I can identify the interviewer and objects in the room easily.
3= Severe, I can barely see things around me, such as the interviewer and the objects in the room.
4= Extreme, I cannot make anything out around me.

19. Do colors seem much brighter than you would have expected?
0= Not at all.
1= Mild, colors seem a little bit brighter than normal, but not more than twice as bright.
2= Moderate, colors seem brighter, about twice as bright as normal.
3= Severe, colors seem very bright, at least five times as bright as normal.
4= Extreme, colors seem extremely bright, almost fluorescent, at least 10 times as bright as normal.

20. Do you feel confused about who you really are?
0= Not at all.
1= Mild, I feel a little bit confused about who I am.
2= Moderate, I feel confused about who I am, but I basically know who I am.
3= Severe, I feel very confused about who I am, and at times I wonder if I am a

person, or if I am many people.

4= Extreme, I feel as if there were two or more sides to myself.

21. Do you feel like there are different parts of yourself which do not fit together?
    - 0= Not at all.
    - 1= Mild, I feel like there are different sides of myself, but they're basically part of myself.
    - 2= Moderate, I feel like I have different parts which don't quite fit together.
    - 3= Severe, there are two or more sides to myself which have unique characteristics.
    - 4= Extreme, I have two or more parts to myself with unique personality characteristics.
22. Do you have gaps in your memory?
    - 0= Not at all.
    - 1= Mild, there are some recent things which I cannot remember.
    - 2= Moderate, there have been a few gaps in my memory which lasted a few minutes.
    - 3= Severe, there have been large gaps in my memory which lasted for more than a few minutes.
    - 4= Extreme, I cannot piece together what is happening from one moment to the next due to large gaps in my memory.
23. Do you feel like you have more than one identity?
    - 0= Not at all.
    - 1= Mild, I feel like there is more to me than my personality, but it's basically part of my identity.
    - 2= Moderate, I feel like I have more than one personality, but the personalities are not really distinct.
    - 3= Severe, I have two or more personalities, although they are not fully developed as distinct entities.
    - 4= Extreme, I have two or more personalities which are distinct and have their own names and other unique characteristics.

## 12.12. Appendix 12: Columbia-Suicide Severity Rating Scale – Baseline/Screening

# COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

*Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.*

*Disclaimer:*

*This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.*

*Definitions of behavioral suicidal events in this scale are based on those used in* ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

*For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu*

| ***SUICIDAL IDEATION*** | | |
|---|---|---|
| *Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.* | **Lifetime: Time He/She Felt Most Suicidal** | **Past Months** |
| **1. Wish to be Dead**<br>Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.<br>***Have you wished you were dead or wished you could go to sleep and not wake up?***<br>If yes, describe: | Yes ☐ No ☐ | Yes ☐ No ☐ |
| **2. Non-Specific Active Suicidal Thoughts**<br>General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.<br>***Have you actually had any thoughts of killing yourself?***<br>If yes, describe: | Yes ☐ No ☐ | Yes ☐ No ☐ |
| **3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act**<br>Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it... and I would never go through with it."*<br>***Have you been thinking about how you might do this?***<br>If yes, describe: | Yes ☐ No ☐ | Yes ☐ No ☐ |
| **4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan**<br>Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*<br>***Have you had these thoughts and had some intention of acting on them?***<br>If yes, describe: | Yes ☐ No ☐ | Yes ☐ No ☐ |
| **5. Active Suicidal Ideation with Specific Plan and Intent**<br>Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.<br>***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?***<br>If yes, describe: | Yes ☐ No ☐ | Yes ☐ No ☐ |
| ***INTENSITY OF IDEATION*** | | |
| *The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.*<br>Lifetime - *Most Severe Ideation:* _____ *Type # (1-5)* _____ *Description of Ideation*<br>Past X Months - *Most Severe Ideation:* _____ *Type # (1-5)* _____ *Description of Ideation* | Most Severe | Most Severe |
| **Frequency**<br>***How many times have you had these thoughts?***<br>(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day | ___ | ___ |
| **Duration**<br>***When you have the thoughts how long do they last?***<br>(1) Fleeting - few seconds or minutes<br>(2) Less than 1 hour/some of the time<br>(3) 1-4 hours/a lot of time<br>(4) 4-8 hours/most of day<br>(5) More than 8 hours/persistent or continuous | ___ | ___ |
| **Controllability**<br>***Could/can you stop thinking about killing yourself or wanting to die if you want to?***<br>(1) Easily able to control thoughts<br>(2) Can control thoughts with little difficulty<br>(3) Can control thoughts with some difficulty<br>(4) Can control thoughts with a lot of difficulty<br>(5) Unable to control thoughts<br>(0) Does not attempt to control thoughts | ___ | ___ |
| **Deterrents**<br>***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?***<br>(1) Deterrents definitely stopped you from attempting suicide<br>(2) Deterrents probably stopped you<br>(3) Uncertain that deterrents stopped you<br>(4) Deterrents most likely did not stop you<br>(5) Deterrents definitely did not stop you<br>(0) Does not apply | ___ | ___ |
| **Reasons for Ideation**<br>***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?***<br>(1) Completely to get attention, revenge or a reaction from others<br>(2) Mostly to get attention, revenge or a reaction from others<br>(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain<br>(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)<br>(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)<br>(0) Does not apply | ___ | ___ |

| *SUICIDAL BEHAVIOR*<br>*(Check all that apply, so long as these are separate events; must ask about all types)* | Lifetime | Past __ Years |
|---|---|---|
| **Actual Attempt:**<br>A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. *There does not have to be any injury or harm*, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.<br>Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.<br>***Have you made a suicide attempt?***<br>***Have you done anything to harm yourself?***<br>***Have you done anything dangerous where you could have died?***<br>***What did you do?***<br>***Did you_____as a way to end your life?***<br>***Did you want to die (even a little) when you_____?***<br>***Were you trying to end your life when you_____?***<br>***Or did you think it was possible you could have died from_____?***<br>***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent)<br>If yes, describe: | Yes ☐ No ☐<br><br>Total # of Attempts<br>_____ | Yes ☐ No ☐<br><br>Total # of Attempts<br>_____ |
| **Has subject engaged in Non-Suicidal Self-Injurious Behavior?** | Yes ☐ No ☐ | Yes ☐ No ☐ |
| **Interrupted Attempt:**<br>When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*.<br>Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.<br>***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?***<br>If yes, describe: | Yes ☐ No ☐<br><br>Total # of interrupted<br>_____ | Yes ☐ No ☐<br><br>Total # of interrupted<br>_____ |
| **Aborted Attempt:**<br>When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.<br>***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?***<br>If yes, describe: | Yes ☐ No ☐<br><br>Total # of aborted<br>_____ | Yes ☐ No ☐<br><br>Total # of aborted<br>_____ |
| **Preparatory Acts or Behavior:**<br>Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).<br>***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?***<br>If yes, describe: | Yes ☐ No ☐ | Yes ☐ No ☐ |
| **Suicidal Behavior:**<br>Suicidal behavior was present during the assessment period? | Yes ☐ No ☐ | Yes ☐ No ☐ |

| *Answer for Actual Attempts Only* | Most Recent Attempt Date: | Most Lethal Attempt Date: | Initial/First Attempt Date: |
|---|---|---|---|
| **Actual Lethality/Medical Damage:**<br>0. No physical damage or very minor physical damage (e.g., surface scratches).<br>1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains).<br>2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel).<br>3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).<br>4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).<br>5. Death | *Enter Code*<br>_____ | *Enter Code*<br>_____ | *Enter Code*<br>_____ |
| **Potential Lethality: Only Answer if Actual Lethality=0**<br>Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).<br>0 = Behavior not likely to result in injury<br>1 = Behavior likely to result in injury but not likely to cause death<br>2 = Behavior likely to result in death despite available medical care | *Enter Code*<br>_____ | *Enter Code*<br>_____ | *Enter Code*<br>_____ |

## 12.13. Appendix 13: Columbia–Suicide Severity Rating Scale - Since Last Visit

# COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit
Version 1/14/09

***Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.***

*Disclaimer:*

*This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.*

*Definitions of behavioral suicidal events in this scale are based on those used in* ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

*For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu*



| ***SUICIDAL IDEATION*** | |
|---|---|
| *Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4, and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.* | Since Last Visit |
| **1. Wish to be Dead**<br>Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.<br>***Have you wished you were dead or wished you could go to sleep and not wake up?***<br>If yes, describe: | **Yes No**<br>☐ ☐ |
| **2. Non-Specific Active Suicidal Thoughts**<br>General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.<br>***Have you actually had any thoughts of killing yourself?***<br>If yes, describe: | **Yes No**<br>☐ ☐ |

| | |
|---|---|
| **3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act**<br>Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place, or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where, or how I would actually do it…and I would never go through with it."*<br>***Have you been thinking about how you might do this?***<br>If yes, describe: | **Yes No**<br>☐ ☐ |
| **4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan**<br>Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*<br>***Have you had these thoughts and had some intention of acting on them?***<br>If yes, describe: | **Yes No**<br>☐ ☐ |
| **5. Active Suicidal Ideation with Specific Plan and Intent**<br>Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.<br>***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?***<br>If yes, describe: | **Yes No**<br>☐ ☐ |
| ***INTENSITY OF IDEATION*** | |
| *The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).*<br>***Most Severe Ideation:*** _____<br>***Type # (1-5) Description of Ideation*** | Most Severe |
| **Frequency**<br>***How many times have you had these thoughts?***<br>(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day | ____ |
| **Duration**<br>***When you have the thoughts, how long do they last?***<br>(1) Fleeting - few seconds or minutes<br>(2) Less than 1 hour/some of the time<br>(3) 1-4 hours/a lot of time<br>(4) 4-8 hours/most of day<br>(5) More than 8 hours/persistent or continuous | ____ |
| **Controllability**<br>***Could/can you stop thinking about killing yourself or wanting to die if you want to?***<br>(1) Easily able to control thoughts<br>(2) Can control thoughts with little difficulty<br>(3) Can control thoughts with some difficulty<br>(4) Can control thoughts with a lot of difficulty<br>(5) Unable to control thoughts<br>(0) Does not attempt to control thoughts | ____ |
| **Deterrents**<br>***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?***<br>(1) Deterrents definitely stopped you from attempting suicide<br>(2) Deterrents probably stopped you<br>(3) Uncertain that deterrents stopped you<br>(4) Deterrents most likely did not stop you<br>(5) Deterrents definitely did not stop you<br>(0) Does not apply | ____ |
| **Reasons for Ideation**<br>***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words, you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge ,or a reaction from others? Or both?***<br>(1) Completely to get attention, revenge or a reaction from others<br>(2) Mostly to get attention, revenge or a reaction from others living<br>(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain<br>(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling).<br>(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)<br>(0) Does not apply | ____ |

| ***SUICIDAL BEHAVIOR***<br>*(Check all that apply, so long as these are separate events; must ask about all types)* | Since Last Visit |
|---|---|
| **Actual Attempt:**<br>A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.<br>Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.<br>***Have you made a suicide attempt?***<br>***Have you done anything to harm yourself?***<br>***Have you done anything dangerous where you could have died?***<br>***What did you do?***<br>***Did you_____ as a way to end your life?***<br>***Did you want to die (even a little) when you_____?***<br>***Were you trying to end your life when you _____?***<br>***Or did you think it was possible you could have died from_____?***<br>***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent)<br>If yes, describe:<br><br>**Has subject engaged in Non-Suicidal Self-Injurious Behavior?** | **Yes No**<br>☐ ☐<br><br>Total # of Attempts<br>_____<br><br>**Yes No**<br>☐ ☐ |
| **Interrupted Attempt:**<br>When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).*<br>Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed, and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.<br>***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?***<br>If yes, describe: | **Yes No**<br>☐ ☐<br><br>Total # of interrupted<br>_____ |
| **Aborted Attempt:**<br>When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.<br>***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?***<br>If yes, describe: | **Yes No**<br>☐ ☐<br><br>Total # of aborted<br>_____ |
| **Preparatory Acts or Behavior:**<br>Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).<br>***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away, or writing a suicide note)?***<br>If yes, describe: | **Yes No**<br>☐ ☐ |
| **Suicidal Behavior:**<br>Suicidal behavior was present during the assessment period? | **Yes No**<br>☐ ☐ |
| **Completed Suicide:** | **Yes No** |

| | ☐ ☐ |
|---|---|
| ***Answer for Actual Attempts Only*** | Most Lethal Attempt Date: |
| **Actual Lethality/Medical Damage:**<br>0. No physical damage or very minor physical damage (e.g., surface scratches).<br>1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains).<br>2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel).<br>3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).<br>4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).<br>5. Death | *Enter Code*<br>_____ |
| **Potential Lethality: Only Answer if Actual Lethality = 0**<br>Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).<br>0 = Behavior not likely to result in injury<br>1 = Behavior likely to result in injury but not likely to cause death<br>2 = Behavior likely to result in death despite available medical care | *Enter Code*<br>_____ |

## 12.14. Appendix 14: Protocol Amendment 1

**Protocol Amendment 1: June 2018**

**Overall Rationale for the Amendment:**
The protocol was amended to provide clarification of the exclusion criteria and of Appendix 5.

| Section No. and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 6.2 Exclusion Criteria | Revised Exclusion Criterion 7 to state: "Lifetime history of nonresponse to ≥ 2 antidepressants after adequate trials (adequate treatment is defined as at least 6 weeks at an adequate dose(s) based on approved package insert recommendations)." | For clarity |
| Section 12.5: Appendix 5 Contraceptive Guidance and Collection of Pregnancy Information | Clarified description of acceptable contraceptive methods. | For clarity |